# Modeling the Dynamics of Bacteremic Pneumonia: The role of Control Strategies, Case Detection and Treatment

by

**Ong'ala, Jacob Otieno**

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**School of Mathematics, Statistics and Actuarial Science**

MASENO UNIVERSITY

## ABSTRACT

Pneumonia is a respiratory disease mainly caused by bacteria, *Streptococcus Pneumoniae*. The bacteria exist in up to 90 different strains out of which 25 are invasive. Pneumonia is one of the leading causes of mortality in the developing countries claiming about 1.9 million lives per year. Deaths due to pneumonia can occur within 3 days of illness and any delay of treatment may not save live. Hence prompt and effective control measures for the disease is needed. Integrating mathematical modeling in epidemiological research is important in studying dynamics and identifying effective control measures. In this study therefore, we developed mathematical models to study the dynamics of pneumonia and assessed the optimal control strategy in a community. The models were analyzed by applying the theory of ordinary differential equations and dynamical systems to determine if there is a point where equilibrium appears, disappears, change stability or conditions necessary for the disease to invade. Finally, a Monte Carlo Markov Chain (MCMC) simulation technique was used to simulate data for transmission parameters when vaccination and treatment are used as control strategies. A kernel density estimation was then used to estimate probability distribution of the transmission parameters. The results show that eliminating carriers in a population is an important strategy in reducing the disease burden since it reduces the value of basic reproduction number, $R_o$. The use of both vaccination and treatment control strategies showed a significant reduction on disease dynamics; however using treatment alone is not significant. Using case detection strategy is important in reducing the disease incidence. A detailed analysis of the simulated transmission data leads to probability distribution of $R_o$ as opposed to a single value in the conventional deterministic modeling approach hence a better estimation for transmission parameter realized. We recommend that at least 22% of the serotype be covered in any vaccine to be used in at least 54% of the population to guarantee efficiency of such vaccination strategies. We also recommend a case detection strategy whenever possible in a population.

# Chapter 1

# INTRODUCTION

## 1.1 Background of the study

Pneumonia is a high-incidence respiratory disease characterized by an inflammatory condition of the lungs and is caused by micro-organisms namely: bacteria, fungi, parasites and viruses. Among the four micro-organisms potential in causing pneumonia, bacteria are reported to be the leading cause (Obaro & Adegbola, 2002; Todar, 2011) especially *Streptococcus Pneumoniae* (Pessoa, 2010; Greenwood, 1999; Rudan et al., 2011). Once the bacteria enter the lungs, they usually settle in the alveoli (air sacs) and passages of the lung where they rapidly grow and multiply in number. The area of the lung that is invaded then becomes filled with fluid and pus (the body's inflammatory cells) as the body attempts to fight off the infection (Schiffman & Melissa, 2010). This makes breathing difficult, painful and limits the intake of oxygen. The disease can occur in all the ages, but have a severe effect on those individuals whose immune systems are compromised or underdeveloped (Greenwood, 1999).

Alongside pneumonia, the bacteria (*Streptococcus Pneumoniae*) can also cause other diseases such as: meningitis, otitis media and acute respiratory infections. These diseases have claimed a significant percentage of lives (Greenwood, 1999). There are more than 90 serotypes of *Streptococcus Pneumoniae* that have been identified (Brueggemann et al., 2003; Pessoa, 2010; Schluger, 2006), however only 15 of these have pathogenic potential (Brueggemann et al., 2003). Studies show that there is a possibility of acquiring more than one type of serotype (Gray et al., 1980) and this condition is referred to as super-colonization. The acquisition of a new serotype peaks

in cold seasons (Gray et al., 1980). When this occurs, the new serotype will dominate (Pessoa, 2010).

Most cases of pneumonia are as a result of inhaling small droplets of coughs or sneezes containing the bacteria. These droplets get into the air when an infected person coughs or sneezes (Schiffman & Melissa, 2010; Todar, 2011). The bacteria can also be carried in the mouth or flora of nasopharynx of a healthy person without causing any harm (Pessoa, 2010; Schiffman & Melissa, 2010; Todar, 2011). Such people are referred to as carriers. When the bacteria finds its way into the lungs, it can invade and cause the infection (Schiffman & Melissa, 2010; Davis, 2010). This is possible when the immunity of the individual is lowered. The incubation period for the infection may vary depending on the individual's immunity, but generally it ranges from 1 to 3 days (Centers for Disease Control, 2010b).

There is limited information on the transmission patterns of the pneumococcal disease in the developing world (Greenwood, 1999), however, it is pointed out that the risk factors associated with the spread of the disease includes: malnutrition, lack of exclusive breastfeeding, indoor pollution, antecedent viral infection amongst others (Greenwood, 1999; Rudan et al., 2011). Other factors that have been postulated to increase the risk of pneumonia cases in developing countries include: low birth weight, socio-demographic factors such as large family size, overcrowding, inappropriate child care practices, short birth interval, low income, low level of parental education and poor housing (Fonseca et al., 1996). A study conducted by Brueggemann et al. (2003) indicated that the spread of pneumococcal disease is associated with increased carriage rates. Carriers plays a major role in the transmission of most infectious diseases (Kalajdzievska & Li, 2011).

## 1.2 Case detection of Pneumonia

Initial observation of population may be the most critical component for the diagnosis of pneumonia (Shamoon et al., 2004). Case detection is of a great importance both for monitoring the epidemiological situation and for forecasting and operational research. Case detection rates may be used as target indicators in public health documents. In most cases, people who develop pneumonia will initially show symptoms of a cold, sneezes, sore throat, cough (sometimes with sputum production) within the first three days, which are then followed by a high fever and shaking chills (Schiffman & Melissa. 2010).

A doctor can suspect pneumonia during examination of the patient when he/she detects a coarse breathing using a stethoscope. However a chest X-ray is usually ordered to confirm the diagnosis of pneumonia. Sputum samples can also be examined under the microscope to detect the bacteria. During this examination, the transfer of the sample to the laboratory should be done very quickly otherwise overgrowth of non-infecting bacteria from the mouth saliva may predominate and compromise the results (Schiffman & Melissa, 2010).

Another way for detecting pneumonia is to perform a blood test that measures white blood cell(WBC) counts (Jamison et al., 2006). This gives a hint as to the severity of pneumonia and whether it is caused by bacteria or any other organism. An increased number of neutrophils and lymphocytes (type of WBC), indicates possible bacterial infections (Schiffman & Melissa, 2010).

Determining the etiology of *Streptococcus Pneumoniae* has been difficult because the current techniques lack sensitivity and specificity (Jamison et al., 2006; Schluger, 2006) likewise it is equally difficult to differentiate between the viral pneumonia and

bacterial pneumonia due to the similarity in their manifestation (Ghafoor et al., 1990). In places where there is endemic malaria, symptom overlap with pneumonia can easily occur leading to mistreatment of pneumonia with anti-malarial drugs rather than appropriate antibiotics (Kallander et al., 2005). As a result of this, the cases of pneumonia have been reported to increase in such areas.

In some situations, a doctor may misread the blood test or X-ray results, and decide on wrong course of treatment. The doctor may also fail to request blood tests or X-rays at all and rely only on the symptoms hence leads to wrong course of treatment. On the other hand, caretakers can resort to home treatment of pneumonia using 'over-the-counter' drugs, probably antimalarial and delaying professional health care for pneumonia. This may lead to high rate of mortality due to pneumonia (Kallander et al., 2008).

## 1.3 Treatment Strategy of Pneumonia

Deaths due to pneumonia can occur within three days of illness and therefore prompt recognition and treatment with an effective drug is crucial. The treatment of pneumococcal diseases has been successful by use of antibiotics such as: penicillin, chloramphenicol for children and erythromycin for those patients who are allergic to penicillin (Brueggemann & Doern, 2000; Jamison et al., 2006). However, a number of studies have indicated that the bacteria develops penicillin resistance, (Brueggemann & Doern, 2000; Starr et al., 2008; Jamison et al., 2006). Other antibiotics that have been used successfully are: amoxicillin and co-trimoxazole which are equally effective for non-severe pneumonia (Catchup Study Group, 2002), though amoxicillin costs twice as much as co-trimoxazole. Over the last decade, there has been a significant impact on the empiric treatment of infections caused by *Streptococcus pneumoniae* due the substantial increasing trend of its resistance to antibiotic drug (Starr et al., 2008). The drug-resistant strains contribute up to 35 % of pneumonia cases (Centers for

Disease Control, 2010a). Despite the availability of drugs to treat pneumonia, high percentage of deaths are still recorded in many parts of developing world. This is highly contributed to by the presence of drug resistance of serotypes.

## 1.4 Vaccination Strategy of Pneumonia

Efforts have been made to reduce the incidence of infections due to *Streptococcus pneumoniae* in high-risk individuals through vaccination (Appelbaum, 2003; Jamison et al., 2006). Hib vaccine used against the pneumococcal diseases, has been proven to have protective efficacy greater than 90% in most industrialized countries since the 80's when it was included in the immunizations programs (Jamison et al., 2006). The available data in developing countries show that, when there was no vaccination with Hib vaccine, a severe effect of the disease was felt (Coen et al., 1998; Adegbola et al., 1999). Two more vaccines for pneumonia (a 23-valent polysaccharide for adults and a 7-valent protein-conjugated polysaccharide for children) have also been in use since their introduction in 1983 and 2000 respectively (Jamison et al., 2006; Schluger, 2006) though there have been substantial argument over their efficacy (Schluger, 2006). In 2010, a new 13-valent Pneumococcal polysaccharide-protein Conjugate Vaccine (PCV13 [Prevnar13]) was licensed to cover for more serotype (Nuorti & Whitney, 2010). The overall efficacy protection of pneumococcal disease covered by the vaccine has ranged from 73% to 94%.

Studies show that pneumonia cases are reduced by 20% when vaccination is used, however it has been faced with a number of challenges of resistance that is always developed by the bacteria. Major development of the vaccines against the bacteria is also proportional to the challenges but yet only 23 strains are covered in the current vaccines.

## 1.5 The burden of pneumonia

Pneumonia is infectious and is known to be one of the leading causes of morbidity and mortality in developing countries with approximately 1.9 millions people dying of the disease per year (Black et al., 2003) translating to 4 individuals dying per minute in the developing countries due to pneumonia. There have been successful results in the management of the infection through early detection and treatment using antibiotics; however, the emergence of drug resistant serotype of the bacteria has made this strategy less effective and costly (Darboe et al., 2010).

Despite the increasing focus to reduce mortality in the developing countries arising from the Millennium Declaration and from the Millennium Development Goal(MDG) 4 of United Nation- (2011), the under-five mortality rate has generated renewed interest in the development of more accurate assessments. Moreover, monitoring the coverage of interventions to control these deaths is crucial if MDG 4 is to be achieved (Rudan et al., 2011). Thus, it is important to establish more accurate predictions of the causes of such deaths during the period of the first 5 years of living.

## 1.6 Mathematical modeling of diseases

The emergence of infectious diseases has continued to be the major causes of suffering and mortality in developing countries despite improved sanitation, use of antibiotics, and vaccination (Hethcote, 2000). A lot of interest has been revived due to the emergence of such infectious diseases.

Mathematical models of infectious diseases have been used to successfully explain the transmission dynamics of many diseases and the use of such models have grown exponentially from mid 20th century (Hethcote, 2000; Mugisha, 2009). In deterministic

models, the population is divided into compartments depending on the disease status giving rise to models such us: Susceptible-Infected-Susceptible (SIS), Susceptible-Exposed-Infected-Recovered (SEIR), Susceptible-Exposed-Infected-Recovered-Susceptible (SEIRS), etc. Hethcote in his paper grouped pneumonia as a disease that can be modeled using either SIS or SIRS models (Hethcote, 2000). This means that models can be developed where pneumonia infected individuals can be considered to have partial immunity hence re-infected or where individuals are considered not have partial immunity. Once an individual has recovered he/she may gain a partial immunity or not hence there is a possibility of reinfection.

When analyzing the dynamics of infectious diseases, mathematical models become crucial tools. The process of formulating such model clarifies assumptions, variables, and parameters. The models also provide conceptual results such as; thresholds, basic reproduction numbers, contact numbers, and replacement numbers for predicting epidemic and endemic. Moreover, "mathematical models and computer simulations can be used as experimental tools for building and testing theories, answering specific questions, assessing quantitative conjectures, determining sensitivities to changes in parameter values, and estimating important parameters from data" (Hethcote, 2000). The transmission characteristics of infectious diseases within communities can be understood well using Mathematical models and this can lead to better approaches to decreasing the transmission of these diseases.

## 1.7 Monte Carlo Simulations

Monte Carlo simulation relies on repeated random sampling and statistical analysis to compute the results. The method is closely related to random experiments for which the specific result is not known in advance. Mathematical models used in describing the interactions in systems using typically depend on number of input

parameters, which when processed through the mathematical formulas in the model, results in one or more outputs(Mason et al., 2008). The outputs of these models are used in prediction of future occurrences of diseases. An example of such outputs is the basic reproduction number that is commonly used in explaining/understanding transmission dynamics of a disease.

The input parameters for the models depend on various external factors. Because of these factors, realistic models are subject to risk from the systematic variation of the input parameters. In deterministic modeling, these variations are not considered. An effective model should take into consideration, the risks associated with various input parameters.

In Monte Carlo simulation, we identify a statistical distribution which can be used as the source for each of the input parameters. Then, we draw random samples from each distribution, which then represent the values of the input variables. For each set of input parameters, we get a set of output parameters. The value of each output parameter is one particular outcome scenario in the simulation run. We collect such output values from a number of simulation runs. Finally, a statistical analysis is performed on the values of the output parameters, to make decisions about the course of action.

## 1.8 Density Estimation

Given any observed /simulated data of any parameter say X, it is possible to study its behaviour when its probability distribution is known. However it might not be very clear which distribution X takes given the set of data. Density estimation is one of the approaches that can be used to identify the probability distribution of a particular random variable given data. Each probability distribution can be uniquely identified by its parameter set, distribution estimation is essentially the same as finding the parameters of a distribution that would generate the given data in question.

The probability distribution of a continuousvalued random variable X is conventionally described in terms of its probability density function (pdf), $f(x)$, from which probabilities associated with X can be determined using the relationship.

$$P(a \leq X \leq b) = \int_a^b f(x)\,dx \tag{1.1}$$

The aim of many investigations is to estimate $f(x)$ from a sample of observations $x_1$, $x_2$,...,$x_n$ . In what follows we will assume that the observations can be regarded as independent realizations of X. A nonparametric approach is used to estimate $f(x)$ to avoid restrictive assumptions made in parametric approach.

One of the most common method of non-parametric density estimation is the kernel density estimation. It make use of a standardized weighting function known as kernel. A brief background of the Kernel density estimation is discussed below:

Let $X$ be a random variable with continuous distribution $F(x)$ and density $f(x) = \frac{d}{dx}F(x)$ The distribution function $F(x)$ is naturally estimated by the Empirical Cumulative distribution Function (ECDF), $\hat{F}(x)$

$$\hat{F}(x) = \frac{1}{n}\sum_{i=1}^{n} I(X_i \leq x) \tag{1.2}$$

where where **I** is the indicator function, given by

$$I\{X_i \leq x\} = \begin{cases} 1 & if \quad X_i \leq x \\ 0 & otherwise \end{cases} \tag{1.3}$$

but

$$\begin{aligned} f(x) &= \tfrac{dF(x)}{dx} \\ &= \lim_{h\to 0} \tfrac{F(x+h-F(x)}{h} \end{aligned} \tag{1.4}$$

$\hat{f}(x)$ can therefore be estimated as a derivative of $\hat{F}(x)$ using;

$$\begin{aligned}
\hat{f}(x) &= \frac{\hat{F}(x+h)-\hat{F}(x-h)}{2h} \\
&= \frac{\frac{1}{n}\sum I(X_i \leq x+h)-\frac{1}{n}\sum I(X_i \leq x+h)}{2h} \\
&= \frac{1}{2hn}\sum I(x-h \leq X_i \leq x+h)) \\
&= \frac{1}{2hn}\sum I(\mid X_i - x \mid \leq h) \\
&= \frac{1}{2hn}\sum I(\mid \frac{X_i-x}{h} \mid \leq 1) \\
&= \frac{1}{hn}\sum \frac{1}{2} I(\mid \frac{X_i-x}{h} \mid \leq 1)
\end{aligned} \tag{1.5}$$

Then $\frac{1}{2}I(\mid \frac{X_i-x}{h} \mid \leq 1) = k(u) = k(\frac{X_i-x}{h})$ is the kernel function and $h$ is the bandwidth This leads to:

$$\hat{f}(x) = \frac{1}{nh}\sum_{i=1}^{n} k\left(\frac{X_i - x}{h}\right) \tag{1.6}$$

The kernel function and bandwidth are always chosen in a way that the optimality is reached. The kernel function that have been proven to be the most optimal is Epanechikov (Hansen, 2009) while the optimal bandwidth is dependent on the order of the kernel function, however optimality is achieved with larger bandwidth for higher orders.

In this work we therefore developed a mathematical model which describe the transmission dynamics, control strategies and the impact of case detection of pneumonia. The models are then used to evaluate the present status of the disease, construct probability distribution of the basic reproduction number and use it to determine the optimality of the vaccination and treatment strategies and also use the model to predict its future potential impact on mortality and morbidity.

## 1.9 Statement of the Problem

Despite major advances in the understanding of the burden and epidemiology of infectious diseases, almost 1.9 million people still die from pneumonia each year in the developing countries, accounting for 20 % of deaths globally (Bryce et al., 2005). In Kenya, pneumonia contributes up to 16 % of mortality (Cousens et al., 2010). It is

evident that the management of the disease is challenging due to the overlap of its symptoms with malaria hence a possibility of mistreatment with antimalarial drugs (Kallander et al., 2008). Deaths due to pneumonia can occur within three days of illness and any delays in proper treatment may not save life. The progress in reducing the mortality rate has been relatively slow in many parts of the developing world (Niessen et al., 2009). However limited work has been done towards developing mathematical models that describes pneumonia transmission dynamics. Notably, most of the existing mathematical models for infectious diseases are deterministic in nature. Therefore, there is need to undertake a research to develop mathematical models by applying probabilistic approach to identify prompt diagnosis and effective treatment then deduce other intervention strategies for pneumonia. For this to be achieved, accurate projections on possibility of epidemic to occur and strategies to put up control measures is required. Mathematical models integrated in epidemiological research are powerful tools in studying transmission dynamics of diseases and to find threshold parameters necessary for the control of the disease.

## 1.10 Objectives of the study

The general objective of this study is to develop a mathematical model to study the transmission dynamics of pneumonia and it's possible treatment/ prevention strategies. The specific objectives include:

1. To determine the conditions necessary for controlling/ reducing pneumonia transmission by analyzing basic pneumonia model.
2. To determine the optimal vaccination and treatments strategies on pneumonia transmission dynamics using the probability distributions of the basic reproduction number.

3. To evaluate the impact of case detection of pneumonia on its transmission dynamics.

## 1.11 Significant of the study

Mathematical models developed here are important in understanding the dynamics of pneumonia. When making making heath decision, policies or strategies of controlling pneumonia in a community, this model will serve as vital tool of reference. The probabilistic modelling approach described here brings in new approach to improve on the deterministic model since probabilistic modelling is more robust and provide more information.

## 1.12 Outline of the Thesis

This thesis is in six chapters which are outlined below:

1. Chapter 1 - The introduction: it discusses the background information of pneumonia, basic concepts and statement of the problem.
2. Chapter 2- Literature Review: Discusses the pervious work done, in disease modelling
3. Chapter 3 - Model 1: Describes the basic pneumonia model when no control strategies are put in place. The possible strategies are highlighted at the discussion section of this chapter.
4. Chapter 4 - Model 2 - Describe a pneumonia transmission model when control strategies (vaccination and treatment) are incorporated into the basic model.
5. Chapter 5 - Model 3 - Describe a pneumonia transmission model with a case detection and its impact in the transmission dynamics.

6. Chapter 6 - Is the conclusion, recommendation and further research

# Chapter 2

# LITERATURE REVIEW

## 2.1 Introduction

A number of researchers have developed and analyzed mathematical models to explain the dynamics of infectious diseases both in children and in adults. However, limited amount of research work has been done to explain the dynamics of pneumonia in children. There are a few literature that explain the transmission dynamics of pneumonia incorporating the risk factors and effect of carriers in transmission dynamics as well as control strategies such as (Darboe et al., 2010; Rudan et al., 2011; Evagelia et al., 2010). Some of the infectious diseases whose transmission dynamics have been explained using related mathematical models are discussed below.

Tuberculosis (TB) which is transmitted in a similar way to pneumonia has been modeled successfully using system of ordinary differential equations (Colijn et al., 2006; Singer & Kirschner, 2004). Two models for TB were presented by Carolyn (2006): A spatial stochastic individual-based model and a set of delayed differential equations encapsulating the same biological assumptions. On their comparison of two different assumptions about partial immunity and exploring the effect of preventive treatment, they argued that seemingly subtle difference in model assumptions can have effects on the biological conclusions. Singer and Kirschner (2004) on the other hand presented an epidemiological model of *Mycobacterium Tuberculosis* infection that included the process of reinfection. The model was analyzed and used numerical simulations to observe the effect of varying levels of reinfection on the qualitative dynamics of the TB epidemic. Their result showed that a threshold level of reinfection existed in all the cases of the model. Beyond the threshold, dynamics of the model are described by a backward bifurcation. This model is in some way similar to the one

discussed here particularly the inclusion of the re-infection into the model. However the pneumonia model developed in this incorporated the effect of case detection in the transmission dynamics

Other mathematical models of infectious diseases having similar transmission dynamics as pneumonia have been studied such as: A study on "Mathematical model of Haemophilus influenzae Type b" by Coen et al.(1998). In the study, a Susceptible-Carrier-Immune-Diseases (SCID) model was used where the immune class in the model corresponds to resistance to infection after being a carrier. The model indicated that Hib carrier propergate the transmission dynamics of disease and also contributes to natural immunity against the disease, and can also recover to join susceptible class again. Their finding indicated that there is a possibility of eliminating the disease if immunization is used. The model that we developed is similar to this, however both infectious and carriers are considered to propagate the transmission of the disease.

The transmission dynamics of cerebrospinal meningitis is in some way quite similar to that of pneumonia, though the assumptions may not be practical for the case of pneumonia disease. A number of studies of epidemiology of pneumonia (Ghosh & Clements, 1992; Ekman et al., 1993; Rosenow, 1920; Ashby & Turkington, 2007; Kalajdzievska & Li, 2011; Rudan et al., 2011; Todar, 2011), shows that there is a chance of reinfection with pneumonia once the patient has recovered from the disease. The force of infection used in the model assumes that the susceptible become carriers due to contact with the carriers and become infected due to contacts with infected individuals. However the model that we develop assumes that new infections are as a results of susceptible contacts with either carriers or infected individuals and any newly infected individuals may change their status from susceptible to either carrier or infected state at different proportions.

## 2.2 Effect of carriers in disease dynamics

Carriers are believed to play an important role in the transmission dynamic of infectious diseases since their presence hinders eradication of these diseases (Kalajdzievska & Li, 2011). A model developed by Kalajdzievska and Li (2011) described the effect of carriers in transmission dynamic of infectious diseases. From the model, it was indicated that testing and increasing awareness of carriers will have much greater impact on the diseases control than increasing vaccination rates. The model indicated that susceptible population can be infected to become a carrier (asymptomatic) or shows symptoms (become infected) though at different rates. Carriers on the other hand can remain on their state for life or develop to show symptoms. The model however did not take into consideration the fact that a recovered individual can gain temporary immunity. Our proposed model incorporates the role of carriers in a similar way, but in addition, we will consider possibility of carriers of *Streptococcus Pneumoniae* acquire temporal immunity after recovery (Ghosh & Clements, 1992; Ekman et al., 1993; Rosenow, 1920). It was strongly supported by Duora *et. al.* (2000) that the presence of carriers of *Streptococcal pyogenes* bacteria makes the population to be highly vulnerable to streptococcal infections.

## 2.3 Modeling the dynamics of Streptococcal infection

Doura et. al (2000) developed two models for the transmission dynamics of streptococcus infection. In the first model, the population was divided into three compartments that is: susceptible (S), infected (I) and carriers(C. In the model, they suggested that susceptible individual can be infected by either carriers or infected individual. The infected individuals could change their status to become a susceptible or a carrier while carrier on the other hand can develop symptoms to become infected. The model assumes that a susceptible individual can only become a carrier or vice versa

by passing through the infected class. The schematic diagram for the first model is shown in Figure 2.1.

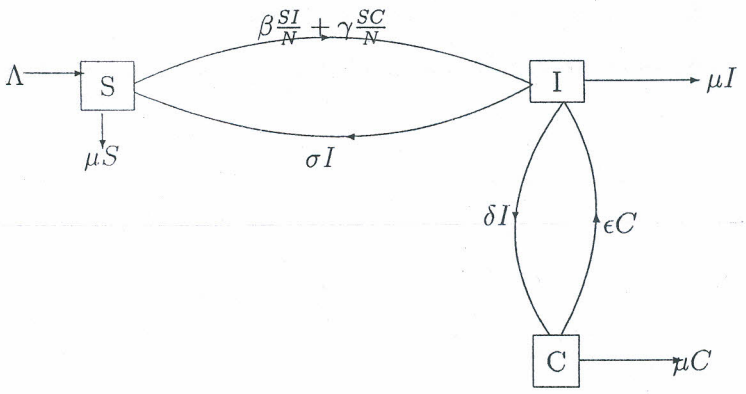


Figure 2.1: First SIS model of Streptococcal disease proposed by Duora et. al. (2000)

The findings of the first model showed that the carrier class is significant in propagating the epidemic. The model that we developed in this study consider that carriers recover from inversion without necessarily being infected. This is referred to as clearing of the bacteria from the body before it invades (Ghosh & Clements, 1992; Ekman et al., 1993; Rosenow, 1920) on the other hand we consider a situation where individual who can change their status from susceptible to carrier without passing through infected class.

In the second model represented by schematic diagram in Figure 2.2 the population was divided into four compartments i.e. susceptible (S), Infected individuals directly from susceptible ($I_s$), Infected individuals directly from carriers ($I_c$) and Carriers (C). In this case the susceptible individual can be infected and return to the susceptible class again without necessarily passing through the carrier class. The model also di-

vides the (I) into Infected susceptible ($I_s$), Infected carriers ($I_c$). It is indicated that the two diseased classes (Infected susceptible ($I_s$) and Infected carriers ($I_c$)) do not have any epidemiological difference apart from the rate at which they transmit the disease (Brueggemann & Doern, 2000; Gray et al., 1980; Greenwood, 1999; Brueggemann et al., 2003; Pessoa, 2010; Fonseca et al., 1996; McKenzie, 1999; Darboe et al., 2010). Hence in our proposed model, we will combine the two classes and refer it to as infected class.

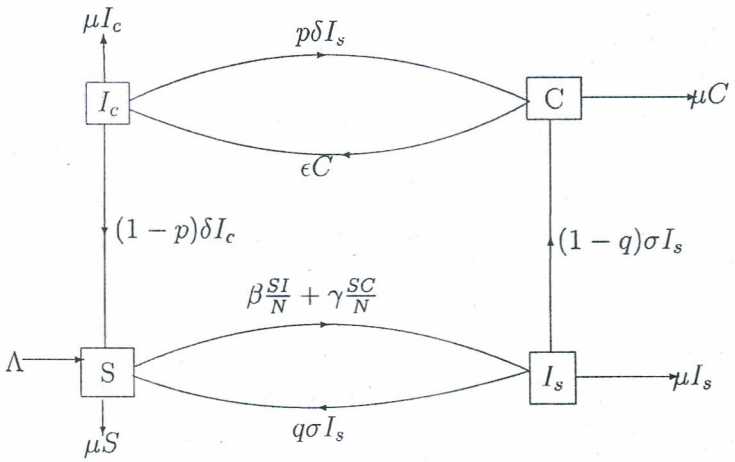


Figure 2.2: Second SIS model of Streptococcal disease proposed by Doura et. al. (2000)

The results of the second model indicated that if the probability of Infected carrier recovering to the carriers class is zero ($p = 0$), then the dynamics of $C \rightarrow I_c$ and $I_c \rightarrow S$ is rapid hence the population is likely to be disease free.

In both models, Doura et. al.(2000) assumed that the individual does not develop immunity to the infection after recovery which is contrary to other findings (Ekman et al., 1993; Ghosh & Clements, 1992; Rosenow, 1920) who strongly supported that once an individual has recovered, they can gain temporary immunity (Ekman et al.,

1993; Ghosh & Clements, 1992).

The model that we develop here uses SIRS-C instead of SIS and incorporate the impact of temporary immunity of the infected and carrier individuals within a population. Despite the availability of the control strategies of streptococcus infections (Appelbaum, 2003; Adegbola et al., 1999; Schluger, 2006), non of the strategies was considered by Daura et. al.(2000) in their model. We build on the model proposed by Daura et. al.(2000) and incorporates the control strategies to assess their impact in the transmission dynamic of the disease.

A stochastic model for pneumonia in children based on a Portuguese day care center was developed by (Pessoa, 2010). In the model, data from a one-year longitudinal on the state of colonization by *Streptococcus pneumoniae* in children attending a day care in Lisboa was used. A conceptual model was built for pneumococcus transmission which considered genotype colonizations and clearance as independents on the number of carriers, the number of non-carriers and the value of four parameters: the clearance rate $\mu$, the within-group transmission parameter $\beta$, the community rate of acquisition $\kappa$ and the between-genotypes competition parameter $\phi$. These parameters were estimated using Bayesian inference. Colonizations and clearances were modeled as Poisson processes and the joint posterior probability distributions of the models parameters were estimated using Markov Chain Monte Carlo sampling. The posterior mean for the transmission parameters were 0.5974 for $\beta$, 0.0107 for $\kappa$, 0.6280 for $\phi$ and 0.3059 for $\mu$ (Pessoa, 2010). Pessoa simulated the data using the posterior estimates.

The model assumed that a child carrying a strain of the bacteria cannot be colonized by the same strain. This assumption is contrary to the approach that we used in our model since from biological literature, it is indicated, that one can be recolonized by the same bacteria (Schiffman & Melissa, 2010). Re-colonization by other genotypes of the bacteria was also taken into consideration in the model, though it had a drawback

since the model did not distinguish between high rates of re-colonizations and low rates of clearance.

## 2.4 Mathematical model for disease dynamics with vaccination

A mathematical model of disease dynamics with vaccination was proposed by Wiah and Adetunde (2010). The model had the population divided into 5 compartments namely: Susceptible, Infected, Carriers, Vaccinated and Recovered (S-C-I-V-R model). A proportion of the susceptible class is vaccinated, however the vaccine may wane or fail to confer immunity to all the vaccinated individuals. Their findings showed that during the initial days, there was a very sharp drop of the susceptible while other populations increased. Many people tend to relax after the initial shock of the disease threat. As people continue to get vaccines the disease is controlled. The model assumed that people cannot be re-infected neither can the infected die of the disease. However we developed a model of transmission with vaccination that also considers reinfection.

Lamb et. al. (2011), developed a simple mathematical model for genetic effects of pneumococcal carriage and transmission. They examined the relationship between the sequence types (genetic material found in the serotype) and serotype where a sequence type is able to manifest itself in one vaccine serotype and one none vaccine serotype. The population under study was subdivided into four compartments: those unvaccinated susceptible to carriage of sequence type 1, those unvaccinated carrying sequence type 1, those vaccinated susceptible to carriage of sequence type 1 and those vaccinated carrying sequence type 1. The model considered only one sequence type and two serotype of streptococcus and assumed that transmission is determined by sequence type but not the serotype and also that the vaccine is wholly effective against

serotype 1 but completely ineffective against serotype 2. This was a simple model and provided a building block for more complex ones.

The improvement of the work of Lamb et. al. (2011) was done by Greenhalgh et. al. (2011). They examined a mathematical model for transmission of *Streptococcus Pneumoniae* amongst young children when the carriage transmission is dependent on serotype. Their model considered two sequence types where each sequence type can manifest itself in two serotype. Their findings indicated that if the effective reproductive number is less than or equal to one, there exists a carriage free equilibrium, and carriage will die out despite starting value. For effective reproductive number more than one, then there exist two carriage equilibria for the two serotype, unless the effective reproductive number of the two serotype are equal. In this study, we model the dynamics with availability of more than two serotype of streptococcus that are responsible for invasion (Brueggemann et al., 2003; Brueggemann & Doern, 2000). We will not consider the effect of sequence type in our model. The availability of vaccines for multiple serotype (Brueggemann & Doern, 2000; Jamison et al., 2006; Schluger, 2006; Coen et al., 1998; Adegbola et al., 1999) motivates this study to model the dynamics of pneumonia with the assumption that all the invasive serotype can be present in the population.

## 2.5 Mathematical model for disease dynamics with treatment

The effective administration of treatment strategy is well understood with mathematical models. Castillo-Chavez and Feng (1995) in their paper formulated one strain and two strain TB models with the aim of determining the possible mechanism that may allow for survival and spread on naturally resistant strain of TB. Their findings indicated that the non-antibiotic co-existence is possible but rare for resistant strains while co-existence was certain with strain that are as a result of lack of compliance

with antibiotic treatment. The model that we developed in this study focus on the effect of mistreatment.

Another model that was suggested by Rosenberg *et al.*,(2007) described how the biological processes taking place within a patient over time can be used to design adaptive treatment strategies. They used the treatment strategies for human immunodeficiency virus Type-1 (HIV) infection. They argued that adaptive treatment strategies is the most promising STI strategies. The model represented how biological mechanisms governing the interaction over time between HIV and a patients immune system and how control methods applied to these models can be used to design adaptive STI strategies seeking to maintain long-term suppression of the virus. Their results indicated that when such mathematical representations of processes underlying a disease or disorder are available, they can be an important tool for suggesting adaptive treatment strategies for clinical studies. The model that developed here assessed the optimal antibiotic administration which is efficient in clearing the bacteria.

In this study therefore we used a deterministic mathematical model that builds on the work of Doura et. al. (2000) for the basic pneumonia model and the work of Wiah and Adetunde (2010) by incorporating control strategies to assess their impact on the transmission dynamic of the disease. These models explains the transmission dynamics of pneumonia, the effects of prophylaxis and its control strategies. We have also used MCMC simulation and Kernel density estimation to assess the transmission parameter.

# Chapter 3

# THE BASIC TRANSMISSION MODEL FOR PNEUMONIA

## 3.1 Introduction

The model formulated here considers the transmission dynamics of pneumonia within population in four compartments (Susceptible, Infected, Carriers and Recovered). The model represent a basic transmission dynamics of pneumonia and does not incorporate any specific prevention strategy. The model is then analyzed to determine the threshold parameters and obtain optimal conditions necessary for controlling pneumonia.

## 3.2 Model Description and Formulation

The basic model is formulated with the population under study being divided into compartments. Based on the model developed by Doura et al. (2000), we will use a SIRS-C framework to describe the disease transmission. This means that the disease can be transmitted between Susceptible, Infectious, Recovered and back to Susceptible again. In some cases the disease is transmitted through Susceptible, Carriers, Infectious, Recovered and back to Susceptible. The total population size at time $t$ denoted $N(t)$ is divided into four compartments according to their disease status namely; Susceptible ($S(t)$), Infected ($I(t)$), Carriers ($C(t)$) and Recovered ($R(t)$). A summary of the variable are described are shown in Table 3.1

Table 3.1: Variables for the basic pneumonia model

| Variable | Description |
|---|---|
| S(t) | Number of susceptible Individuals |
| I(t) | Number of Infected Individuals |
| C(t) | Number of Carrier Individuals |
| R(t) | Number of Recovered Individuals |

The susceptible population can be increased by new recruitment of individuals through either birth or immigration at a rate $\nu$ or when the recovered infective individuals lose their immunity and rejoin the susceptible. We assume that all the individuals who are recruited into the population exclude the infected immigrants because most people who are sick do not travel. The susceptible can either be infected by either carriers or by symptomatically infected individual with a force of infection $\lambda$. A newly infected individual can either become a carrier with a probability $\rho$ or show disease symptoms with a probability $(1-\rho)$. The carriers can develop disease symptoms and become symptomatically infectious (McKenzie, 1999) at a rate $\pi$ or recover to gain immunity against the bacteria at an average rate $\beta$. The infected individuals on the other hand can recover at a percapita rate of $\eta$ or die from the disease at a rate $\alpha$. However recovery of the infected individuals may result to completely clearing all the bacteria from the body with a probability $q$ to gain immunity against the bacteria or changing their status to asymptomatic state (carrier state) after infection period with a probability $(1-q)$ (Tacio, 2011; Division of Disease Control, 2006). Since the immune developed is temporary, there is a chance of reinfection according to research by (Ghosh & Clements, 1992; Ekman et al., 1993; Rosenow, 1920). The rate of losing the immunity is denoted by $\delta$. We denote the natural percapita mortality rate by $\mu$. The natural percapita mortality rate is assumed to be the same in all the classes. The parameters described here are summarized in Table 3.2.

Table 3.2: Description of the parameters used in the basic pneumonia model

| Parameter | Description |
|---|---|
| $\nu$ | Recruitment rate into the susceptible class |
| $\lambda$ | Force of infection due to Carriers |
| $\rho$ | Probability of a newly infected individual being a Carrier |
| $\pi$ | Rate at which Carriers become symptomatically infectious |
| $\eta$ | Rate of recovery from the symptomatically infectious |
| $q$ | Probability of gaining temporary immunity after recovering from infectious class. |
| $\alpha$ | Per capita disease-induced death rate |
| $\delta$ | Per capita rate of loss of immunity |
| $\mu$ | Per capita death rate |
| $\beta$ | Recovery rate of carriers and gaining partial immunity |

Using the variables in Table 3.1 parameters described in Table 3.2, we represent the disease transmission using (3.1)

$$\left.\begin{aligned} \frac{dS(t)}{dt} &= \nu + \delta R(t) - (\lambda + \mu)S(t) \\ \frac{dI(t)}{dt} &= (1-\rho)\lambda S(t) + \pi C(t) - (\mu + \alpha + \eta)I(t) \\ \frac{dC(t)}{dt} &= \rho\lambda S(t) + (1-q)\eta I(t) - (\mu + \pi + \beta)C(t) \\ \frac{dR(t)}{dt} &= q\eta I(t) + \beta C(t) - (\mu + \delta)R(t) \end{aligned}\right\} \tag{3.1}$$

Let $\kappa$ be the contact rate and $\mathcal{P}$ be the probability that a contact is effective to cause an infection. Then, the force of infection $\lambda$ is given by;

$$\lambda = \psi\left(\frac{I(t) + \varepsilon C(t)}{N(t)}\right) \tag{3.2}$$

where $\psi = \kappa\mathcal{P}$ is the effective contact rate and $\varepsilon \leq 1$ account for the relative infectiousness of individuals in the Carriers ($C$) class in comparison to those in the infectious ($I$) class (Doura et al., 2000) and $\psi$ is the efficient contact rate given by

$\psi = \kappa\mathcal{P}$

Substituting (3.2) into (3.1), we obtain,

$$\left.\begin{aligned}
\frac{dS(t)}{dt} &= \nu + \delta R(t) - \psi\frac{I(t)}{N(t)}S(t) - \psi\varepsilon\frac{C(t)}{N(t)}S(t) - \mu S(t)\\
\frac{dI(t)}{dt} &= (1-\rho)\psi\frac{I(t)}{N(t)}S(t) + (1-\rho)\psi\varepsilon\frac{C(t)}{N(t)}S(t) + \pi C(t) - (\mu+\alpha+\eta)I(t)\\
\frac{dC(t)}{dt} &= \rho\psi\frac{I(t)}{N(t)}S(t) + \rho\psi\varepsilon\frac{C(t)}{N(t)}S(t) + (1-q)\eta I(t) - (\mu+\pi+\beta)C(t)\\
\frac{dR(t)}{dt} &= q\eta I(t) + \beta C(t) - (\mu+\delta)R(t)
\end{aligned}\right\} \quad (3.3)$$

The compartmental diagram that corresponds to (3.1) is shown in Figure 3.1.

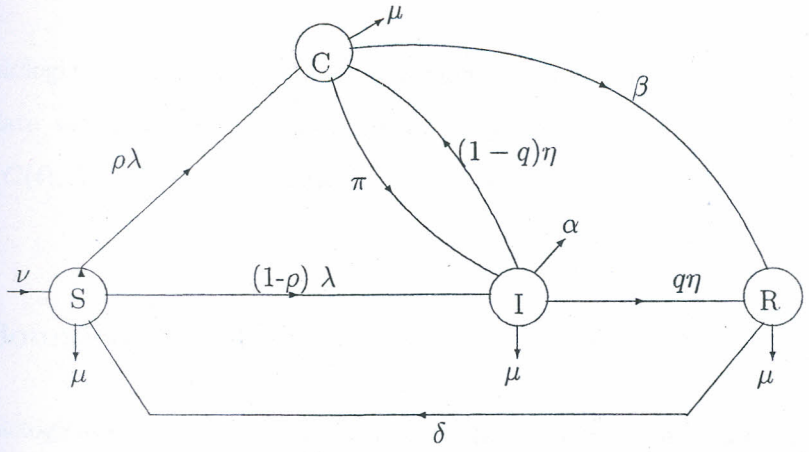


Figure 3.1: Basic compartmental model for pneumonia transmission

The total population size $N(t)$ can be determined using (3.4). The rate of change of the population size is determined by adding all the equations in (3.3) resulting to (3.5)

$$N(t) = S(t) + I(t) + C(t) + R(t) \quad (3.4)$$

$$\left.\begin{aligned}
\frac{dN(t)}{dt} &= \frac{dS(t)}{dt} + \frac{dI(t)}{dt} + \frac{dC(t)}{dt} + \frac{dR(t)}{dt}\\
\frac{dN(t)}{dt} &= \nu - \alpha I(t) - \mu N(t)
\end{aligned}\right\} \quad (3.5)$$

We assume that all the state variables and parameters of the model which monitors the transmission dynamics are positive at time $t$ ($\forall t > 0$), and will therefore be

analyzed in a suitable region. The variables in Table 3.1 have the initial conditions given by:

$$\left.\begin{aligned} S(0) &= S_0 \geq 0 \\ I(0) &= I_0 \geq 0 \\ C(0) &= C_0 \geq 0 \\ R(0) &= R_0 = 0 \\ N(0) &= N_0 \geq 0 \end{aligned}\right\} \tag{3.6}$$

## 3.3 Analysis of the Basic model

To make biological sense, the human populations described in (3.1) at various associated state variables are non-negative for all time $t \geq 0$. Then solution set $\{S(t), I(t), C(t), R(t), N(t)\}$ is positive for all $t \geq 0$

### 3.3.1 Boundedness of Solutions

Based on biological considerations, (3.1) will be studied in the following region:

$\mathcal{G} = \{(S(t), I(t), C(t), R(t)) \in \mathbb{R}^4_+ : 0 \leq N(t) \leq \frac{\nu}{\mu}\}$

The solutions for (3.1) are contained in the region $\mathcal{G}$ since

$$\left.\begin{aligned} &\tfrac{dN(t)}{dt} = \nu - \alpha I(t) - \mu N(t) \\ &\Rightarrow \tfrac{dN(t)}{dt} \leq \nu - \mu N(t) \\ &\Rightarrow N(t) \leq \tfrac{\nu}{\mu} + (N_0 - \tfrac{\nu}{\mu})e^{-\mu t}) \end{aligned}\right\} \tag{3.7}$$

Then, as $t \to \infty$, we have

$$\left.\begin{aligned} &\lim_{t\to\infty} N(t)N(t) \leq \lim_{t\to\infty} N(t)\tfrac{\nu}{\mu} + (N_0 - \tfrac{\nu}{\mu})e^{-\mu t}) \\ &\Rightarrow \lim_{t\to\infty} N(t) \leq \tfrac{\nu}{\mu} \end{aligned}\right\} \tag{3.8}$$

Using results in (3.8) and the fact that $N(t) \geq 0$ at any time t, we have

$$0 \leq N(t) \leq \frac{\nu}{\mu} \tag{3.9}$$

which implies that N(t) is bounded and all the solutions starting in $\mathcal{G}$ approach, enter or stay in $\mathcal{G}$.

### 3.3.2 Basic reproduction number $R_0$

The basic reproduction number is defined as the average number of secondary cases produced by a single infectious individual over his infectious period in an entire susceptible population denoted as $R_0$. The next generation operator method (Driessche & Watmough, 2002; Diekmann et al., 1990; Diekmann & Heesterbeek, 2000) is used to calculate the basic reproductive number. As described by (Driessche & Watmough, 2002), rearranging the equations in (3.3) beginning with the diseased classes I and C followed by the uninfected classes S and R, we obtain system (3.10)

$$\left.\begin{aligned}
\tfrac{dI(t)}{dt} &= (1-\rho)\psi\tfrac{I(t)}{N(t)}S(t) + (1-\rho)\psi\varepsilon\tfrac{C(t)}{N(t)}S(t) + \pi C(t) - (\mu+\alpha+\eta)I(t)\\
\tfrac{dC(t)}{dt} &= \rho\psi\tfrac{I(t)}{N(t)}S(t) + \rho\psi\varepsilon\tfrac{C(t)}{N(t)}S(t) + (1-q)\eta I(t) - (\mu+\pi+\beta)C(t)\\
\tfrac{dS(t)}{dt} &= \nu + \delta R(t) - \psi\tfrac{I(t)}{N(t)}S(t) - \psi\varepsilon\tfrac{C(t)}{N(t)}S(t) - \mu S(t)\\
\tfrac{dR(t)}{dt} &= q\eta I(t) + \beta C(t) - (\mu+\delta)R(t)
\end{aligned}\right\} \tag{3.10}$$

Let $\mathcal{F}_i$ be the rate of appearance of new infections into the class or compartment $i$ and $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ , where $\mathcal{V}_i^-$ is the rate of transfer of individuals out of compartment $i$, and $\mathcal{V}_i^+$ is the rate of transfer of individuals into compartment $i$ by all other. The difference $(\mathcal{F}_i - \mathcal{V}_i)$ is the rate of transfer in compartment $i$. Lets also define, $h_1$ to be the rate of transfer of individuals out of infectious class and $h_2$ be the rate of transfer of individuals out of Carrier class where; $h_1 = \mu + \alpha + \eta$ and $h_2 = \mu + \pi + \beta$.

Then,

$$\mathcal{F}_i = \begin{pmatrix} (1-\rho)\psi I + (1-\rho)\psi\varepsilon C \\ \\ \rho\psi I + \rho\varepsilon\psi C \end{pmatrix} \tag{3.11}$$

$$\mathcal{V}_i = \begin{pmatrix} h_1 I - \pi C \\ \\ h_2 C - (1-q)\eta I \end{pmatrix} \tag{3.12}$$

F, and V can now be computed by finding the partial derivative of the elements in the $\mathcal{F}_i$ and $\mathcal{V}_i$ respectively with respect to I and C as shown in (3.13) and (3.14).

$$\mathbf{F} = \begin{pmatrix} (1-\rho)\psi & (1-\rho)\psi\varepsilon \\ \\ \rho\psi & \rho\psi\varepsilon \end{pmatrix} \tag{3.13}$$

$$\mathbf{V} = \begin{pmatrix} h_1 & -\pi \\ \\ -(1-q)\eta & h_2 \end{pmatrix} \tag{3.14}$$

$FV^{-1}$ is computed as (3.15)

$$FV^{-1} = \begin{pmatrix} \frac{\psi(1-\rho)[h_2+(1-q)\varepsilon\eta]}{h_1h_2-(1-q)\pi\eta} & \frac{\psi(1-\rho)[\pi+\varepsilon h_1]}{h_1h_2-(1-q)\pi\eta} \\ \\ \frac{\rho\psi[h_2+(1-q)\varepsilon\eta]}{h_1h_2-(1-q)\pi\eta} & \frac{\rho\psi[\pi+\varepsilon h_1]}{h_1h_2-(1-q)\pi\eta} \end{pmatrix} \tag{3.15}$$

The eigenvalues of the matrix $FV^{-1}$ are;

$$\left\{0, \psi\left(\frac{\rho[\varepsilon h_1+\pi]+(1-\rho)[h_2+(1-q)\varepsilon\eta]}{h_1h_2-(1-q)\pi\eta}\right)\right\} \tag{3.16}$$

Now $R_0$ is obtained by definition as the spectral radius (dominant eigenvalue) of the matrix $FV^{-1}$. In other words, it is the absolute largest value of $FV^{-1}$.

$$R_o = \psi\left(\frac{\rho[\varepsilon h_1+\pi]+(1-\rho)[h_2+(1-q)\varepsilon\eta]}{h_1h_2-(1-q)\pi\eta}\right) \tag{3.17}$$

The $R_0$ above represents the total number of secondary pneumonia infections caused by a single infected individual introduced into an entirely susceptible group. It is

directly proportional to the effective rate of contact $\psi$ and it consist of two terms. The first term is $\psi\left(\frac{\rho[\varepsilon h_1+\pi]}{h_1h_2-(1-q)\pi\eta}\right)$ which represents the number of secondary infections caused by one carrier in a population and $\psi\left(\frac{(1-\rho)[h_2+(1-q)\varepsilon\eta]}{h_1h_2-(1-q)\pi\eta}\right)$ which represent the number of secondary infections caused by one infected individual in a population.

The value of $R_o < 1$ is an indication that a disease will possibly be controlled. Therefore a strategy of reducing the number of new secondary infections by reducing the value of the basic reproduction number, $R_0$ may be considered. Rewriting (3.17) as,

$$R_0 = \kappa\mathcal{P}\left(\frac{\rho[\varepsilon(\mu+\alpha+\eta)+\pi]+(1-\rho)[\mu+\beta+\pi+(1-q)\varepsilon\eta]}{(\mu+\alpha+\eta)(\mu+\beta+\pi)-(1-q)\pi\eta}\right),$$

is an evidence that $R_0$ is directly proportional to the contact rate $\kappa$ and to the mean time spent in the diseased classes. $\frac{1}{(\mu+\alpha+\eta)(\mu+\beta+\pi)-(1-q)\pi\eta}$. The implication of reducing the contact rate i.e. $\kappa \to 0$ and mean time spent in the diseased classes ensures that the basic reproduction number reduces towards zero, $R_0 \to 0$. It is possible to reduce mean time spent in the diseased classes when the transfer rates between the Carrier and the Infected classes are reduced (i.e. $\pi \to 0$ and $q \to 1$) and when the transfer rate out from the diseased classes are increased (i.e. $\eta, \beta \to \infty$). This indicates that quarantine (where possible), prompt and effective case detection and treatment of carriers and infected individuals may lead to possible reduction of the new infections to zero.

### 3.3.3 Equilibrium states of the system

Let $E = \{S^*, I^*, C^*, R^*\}$ be a set of solution at the equilibrium point for (3.3). Then at equilibrium points, we equate the right hand side of the equations in (3.3) to zeros

obtaining (3.18)

$$\left.\begin{aligned}
\nu + \delta R(t) - \psi\tfrac{I(t)}{N(t)}S(t) - \psi\varepsilon\tfrac{C(t)}{N(t)}S(t) - \mu S(t) &= 0\\
(1-\rho)\psi\tfrac{I(t)}{N(t)}S(t) + (1-\rho)\psi\varepsilon\tfrac{C(t)}{N(t)}S(t) + \pi C(t) - (\mu+\alpha+\eta)I(t) &= 0\\
\rho\psi\tfrac{I(t)}{N(t)}S(t) + \rho\psi\varepsilon\tfrac{C(t)}{N(t)}S(t) + (1-q)\eta I(t) - (\mu+\pi+\beta)C(t) &= 0\\
q\eta I(t) + \beta C(t) - (\mu+\delta)R(t) &= 0
\end{aligned}\right\} \quad (3.18)$$

When system (3.18) is solved simultaneously, it has two equilibrium points namely: the disease-free equilibrium and the endemic equilibrium point.

We denote the disease-free equilibrium (DFE) by $E_o$ and it is defined as a steady state solutions of (3.18) when there is absence of disease *i.e.* (the diseased classed (infectious and the carriers) are equal to zero, hence

$$E_o = \left(\frac{\nu}{\mu}, 0, 0, 0\right) \quad (3.19)$$

To obtain the endemic equilibrium $E^e$ of the System (3.3), we solve the system (3.18) and obtain $E^e = \{S^e, I^e, C^e, R^e\}$ which can be expressed in terms of $R_o$ as shown in (3.20)

$$\left.\begin{aligned}
S^e &= \frac{N}{R_o}\\
C^e &= \frac{(\mu+\delta)((1-\rho)(1-q)\eta+h_1\rho)(R_o-1)\nu}{R_o((\mu+\delta)(h_2h_1-(1-q)\pi\eta)-\delta(\rho(\eta\pi q+h_1\beta)+(1-\rho)(\eta q h_2+(1-q)\eta\beta)))}\\
I^e &= \frac{(\delta+\mu)(\pi\rho+(1-\rho)h_2)(R_o-1)\nu}{R_o((\delta+\mu)(h_2h_1-(1-q)\pi\eta)-\delta(\rho(\pi q\eta+h_1\beta)+(1-\rho)(\eta q h_2+(1-q)\eta\beta)))}\\
R^e &= \frac{(\rho(\eta\pi q+h_1\beta)+(-\rho+1)(h_2q\eta+(1-q)\eta\beta))(R_o-1)\nu}{R_o((\delta+\mu)(h_2h_1-(1-q)\pi\eta)-\delta(\rho(\pi q\eta+h_1\beta)+(1-\rho)(\eta q h_2+(1-q)\eta\beta)))}
\end{aligned}\right\} \quad (3.20)$$

### Uniqueness of the Equilibrium states

When we substitute the set of solutions of $E_o$ into (3.3), we obtain similar results as in (3.18), hence DFE is an equilibrium point.

It is easy to show that the endemic equilibrium in (3.20)is indeed unique when $R_0 > 1$. Consider

$$\begin{aligned} (1-\rho)\psi\tfrac{S}{N}(I+\varepsilon C) + \pi C - h_1 I > 0 \\ \rho\psi\tfrac{S}{N}(I+\varepsilon C) + (1-q)\eta I - h_2 C > 0 \end{aligned} \tag{3.21}$$

From the first inequality of (3.21) we have that

$$h_1 I < (1-\rho)\psi\tfrac{S}{N}(I+\varepsilon C) + \pi C$$

using the fact $\frac{S}{N} \leq 1$

$$I < \frac{(1-\rho)\psi I + (1-\rho)\psi\varepsilon C + \pi C}{h_1} \tag{3.22}$$

and from the second inequality of (3.21) we have that

$$C < \frac{\rho\psi I + (1-q)\eta I}{h_2 - \rho\psi\varepsilon} \tag{3.23}$$

substituting (3.23) into (3.22), we have that

$$I < \frac{(1-\rho)\psi I + [(1-\rho)\psi\varepsilon + \pi]\left[\frac{\rho\psi I + (1-q)\eta I}{h_2 - \rho\psi\varepsilon}\right]}{h_1}$$

*Thatis*

$$1 < \frac{(1-\rho)\psi I + [(1-\rho)\psi\varepsilon + \pi][\rho\psi I + (1-q)\eta I]}{h_1 h_2 - h_1\rho\psi\varepsilon} \tag{3.24}$$

*Thatis*

$$h_1 h_2 - h_1\rho\psi\varepsilon < (1-\rho)\psi h_2 + \rho\psi\pi + (1-\rho)\psi\varepsilon(1-q)\eta + (1-q)\eta\pi$$

$$1 < \frac{\psi[\rho(h_1\varepsilon + \pi) + (1-\rho)(h_2 + (1-q)\varepsilon\eta)]}{h_1 h_2 - (1-q)\eta\pi} = R_0$$

$$R_0 > 1$$

Thus a unique endemic equilibrium exist when $R_0 > 1$ .

## 3.4 Stability Analysis

In stability analysis, we examine the long term behavior of the spread of disease. In particular, we look for conditions necessary for persistence and eradication of the disease.

### 3.4.1 Local stability of the disease-free equilibrium $E_o$

We prove the local stability of the disease free equilibrium by stating and proving Lemma 3.4.1

**Lemma 3.4.1** *(Castillo-Chavez & Song, 2004), The the disease-free equilibrium ($E_o$) of (3.25) below is locally asymptotically stable whenever $R_0 < 1$ and unstable when $R_0 > 1$.*

$$\left.\begin{aligned}
\frac{dS(t)}{dt} &= \nu + \delta R(t) - \psi\frac{I(t)}{N(t)}S(t) - \psi\varepsilon\frac{C(t)}{N(t)}S(t) - \mu S(t)\\
\frac{dI(t)}{dt} &= (1-\rho)\psi\frac{I(t)}{N(t)}S(t) + (1-\rho)\psi\varepsilon\frac{C(t)}{N(t)}S(t) + \pi C(t) - (\mu+\alpha+\eta)I(t)\\
\frac{dC(t)}{dt} &= \rho\psi\frac{I(t)}{N(t)}S(t) + \rho\psi\varepsilon\frac{C(t)}{N(t)}S(t) + (1-q)\eta I(t) - (\mu+\pi+\beta)C(t)\\
\frac{dR(t)}{dt} &= q\eta I(t) + \beta C(t) - (\mu+\delta)R(t)
\end{aligned}\right\} \quad (3.25)$$

**Proof** Consider the jacobian matrix for the Model (3.3) at $E_o$ is given as

$$\mathcal{J}(E_o) = \begin{pmatrix} -\mu & -\psi & -\psi\varepsilon & \delta \\ 0 & -h_1 & \pi & 0 \\ 0 & (1-q)\eta & -h_2 & 0 \\ 0 & q\eta & \beta & -(\mu+\delta) \end{pmatrix} \text{ and}$$

$$\left.\begin{aligned}
Trace\left[\mathcal{J}(E_o)\right] &= -(2\mu+\delta+h_1+h_2) < 0\\
Det\left[\mathcal{J}(E_o)\right] &= \mu(\delta+\mu)[h_1h_2 - (1-q)\pi\eta] > 0
\end{aligned}\right\} \quad (3.26)$$

Since the parameters $\mu, \delta, h_1$ and $h_2$ are all positive, then $-(2\mu+\delta+h_1+h_2) < 0$. Therefore $Trace\left[\mathcal{J}(E_o)\right] < 0$. On the other hand $Det\left[\mathcal{J}(E_o)\right]$ can be expressed as:

$$Det\left[\mathcal{J}(E_o)\right] = \mu(\delta+\mu)\left[\frac{\psi(\rho[\varepsilon h_1+\pi] + (1-\rho)[h_2+(1-q)\varepsilon\eta])}{R_o}\right] \quad (3.27)$$

But, $R_0$ can never be negative and numerator $\{\rho[\varepsilon h_1+\pi]+(1-\rho)[h_2+(1-q)\varepsilon\eta]\}$ is positive. This implies that $Det\left[\mathcal{J}(E_o)\right] > 0$, since $\mu(\delta+\mu) > 0$ and $[h_1h_2-(1-q)\pi\eta] > 0$.

The solutions in (3.26) implies that $E_o$ is locally asymptotically stable whenever $R_0 < 1$

### 3.4.2 Global asymptotic stability of the disease-free equilibrium $E_o$

For a global stability we use the theorem by Castillo-Chavez & Song (2004). We rewrite the system (3.1) as:

$$\begin{aligned} \frac{dX}{dt} &= T(X,Z) \\ \frac{dZ}{dt} &= G(X,Z), G(X,0) = 0 \end{aligned} \tag{3.28}$$

where $X = (S, R)$ and $Z = (I, C)$ with $X \in \mathbb{R}^2$ denoting the number of uninfected individuals including the susceptible and recovered and $Z \in \mathbb{R}^2$ denoting the number of infected individuals including the carriers and infectious and $E_o$ denote the disease free equilibrium given by

$$E_o = (X^*, 0), X^* = \left(\frac{\nu}{\mu}, 0\right) \tag{3.29}$$

The following are the conditions that must be met for global asymptotic stability.

1. For $\frac{dX}{dt} = T(X, 0)$, $X^*$ is global asymptotic stability (GAS)

2. $G(X, Z) = HZ - \hat{G}(X, Z), \hat{G}(X, Z) \geq 0 for (X, Z) \in \mathcal{G}_2$

where $H = D_z G(X^*,0)$ is an Metzler Matrix, and G is the region where the model make biological sense, If the system (3.28) satisfies the conditions above, then theorem below holds.

**Theorem 3.4.2** *(Castillo-Chavez & Song, 2004) The disease free equilibrium is a globally asymptotically stable equilibrium of system (3.28) provided $R_o \leq 1$ (l.a.s) that the two conditions above are satisfied.*

Proof If the model (3.1) is re-written as 3.28 then

$$T(X, 0) = \begin{bmatrix} \nu - \mu S \\ 0 \end{bmatrix} \tag{3.30}$$

$$G(X, Z) = HZ - \hat{G}(X, Z), \tag{3.31}$$

$$H = \begin{bmatrix} (1-\rho)\psi - (\mu+\alpha+\eta) & (1-\rho)\psi\epsilon + \pi \\ \rho\epsilon + (1-q)\eta & \epsilon\psi\rho - (\mu+\pi+\beta) \end{bmatrix} \tag{3.32}$$

Then

$$\hat{G}(X,Z) = \begin{bmatrix} \left(1-\frac{S}{N}\right)(1-\rho)\,\psi\ (\epsilon C + F) \\ \left(1-\frac{S}{N}\right)\rho\,\psi\ (\epsilon C + F) \end{bmatrix} \tag{3.33}$$

Since $\frac{S}{N} \leq 1$ Then $\hat{G}(X,Z) > 0$. The two conditions are met.

### 3.4.3 Bifurcation analysis and Local Stability of the Endemic Equilibrium

A bifurcation is a qualitative change in the nature of the solution trajectories due to a parameter change. The point at which this change takes place is called a bifurcation point. At the bifurcation point, a number of equilibrium points, or their stability properties, or both, change. When $R_0 < 1$, the infectious disease will not invade the population unless otherwise. We prove by using Center Manifold theorem the possibility of bifurcation at $R_0 = 1$.



Let $S = x_1, I = x_2, C = x_3$ and $R = x_4$, so that $N = x_1 + x_2 + x_3 + x_4$, then System (3.10) is re-written in the form:

$$\left.\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \nu + \delta x_4 - \psi\frac{x_2}{x_1+x_2+x_3+x_4}x_1 - \psi\varepsilon\frac{x_3}{x_1+x_2+x_3+x_4}x_1 - \mu x_1 \\
\frac{dx_2}{dt} &= f_2 = (1-\rho)\psi\frac{x_2}{x_1+x_2+x_3+x_4}x_1 + (1-\rho)\psi\varepsilon\frac{x_3}{x_1+x_2+x_3+x_4}x_1 + \pi x_3 - h_1 x_2 \\
\frac{dx_3}{dt} &= f_3 = \rho\psi\frac{x_2}{x_1+x_2+x_3+x_4}x_1 + \rho\psi\varepsilon\frac{x_3}{x_1+x_2+x_3+x_4}x_1 + (1-q)\eta x_2 - h_2 x_3 \\
\frac{dx_4}{dt} &= f_4 = q\eta x_2 + \beta x_3 - (\mu+\delta)x_4
\end{aligned}\right\} \tag{3.34}$$

Suppose that we choose $\psi_c$ as a bifurcation parameter. Then by using (3.17), we solve

$\psi_c$ at $R_0 = 1$ as:

$$\psi_c = \frac{\mu^2 + \mu\alpha + \mu\eta + \pi\mu + \pi\alpha + \beta\mu + \beta\alpha + \beta\eta + \eta q\pi}{\rho\epsilon\mu + \rho\epsilon\alpha + \mu + \pi + \beta + \epsilon\eta - \epsilon\eta q - \rho\mu - \rho\beta + \rho\epsilon\eta q} \tag{3.35}$$

The linearization matrix of (3.34) at a disease free Equilibrium ($E_o$) corresponding to $\psi = \psi_c$ is given by:

$\mathcal{J}(E_o)\,|_{\psi=\psi_c} = J_{\psi_c}$ where

$$J_{\psi_c} = \begin{bmatrix} -\mu & -\psi_c & -\psi_c\varepsilon & \delta \\ 0 & -\mu-\alpha-\eta+(1-\rho)\psi_c & \pi+(1-\rho)\psi_c\varepsilon & 0 \\ 0 & (1-q)\eta+\rho\psi_c & -\beta-\pi-\mu+\rho\psi_c,\varepsilon & 0 \\ 0 & q\eta & \beta & -\mu-\delta \end{bmatrix}$$

It is evident that zero is a simple eigenvalue of $J_{\psi_c}$ . A right eigenvector ($w$) of $J_{\psi_c}$ associated with the zero eigenvalues is then computed as $w = (w_1, w_2, w_3, w_4)^T$ where

$$\begin{aligned} w_1 &= -\frac{(\mu(\delta+\mu+\alpha)(\beta+\pi+\mu)+\mu\eta(\mu+\beta+\delta(\rho q+1-q)+\pi q)+\delta\alpha(\mu+\pi+\beta-\rho\beta)-\delta\beta\rho\mu)w_3}{(\alpha\rho+(\rho q+1-q)\eta+\rho\mu)(\mu+\delta)\mu}w_3 \\ w_2 &= \frac{(\pi+(1-\rho)(\mu+\beta))}{\rho(\alpha+\mu)+(\rho q+1-q)\eta}w_3 \\ w_3 &= w_3 \\ w_4 &= \frac{(\eta(\beta+\pi q+\mu q(1-\rho))+\rho\beta(\alpha+\mu))}{(\mu+\delta)(\rho(\alpha+\mu)+(\rho q+1-q)\eta)}w_3 \end{aligned}$$

and a left eigenvector ($v$) of $J_{\psi_c}$ corresponding to the zero eigenvalues is given by $v = (v_1, v_2, v_3, v_4)^T$ where

$$\begin{aligned} v_1 &= 0 \\ v_2 &= \frac{((1-q)\varepsilon\eta+\mu+\pi+\beta)}{\epsilon\eta+\pi+\epsilon\alpha+\mu\varepsilon}v_3 \\ v_3 &= v_3 \\ v_4 &= 0 \end{aligned}$$

We now reproduce the theorem stated by Castillo-Chavez and Song (2004) .

**Theorem 3.4.3** *(Castillo-Chavez & Song, 2004). Consider the following general system of ordinary differential equations with parameter $\phi$*

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \text{ and } f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R})$$

*where 0 is an equilibrium point of the system ( that is $f(0, \phi) \equiv 0$ for all $\phi$) and assume:*

1. *$A = D_x f(0,0) = (\frac{\partial f_i}{\partial x_j}(0;0))$ is the linearization matrix of the system around the equilibrium point 0 with $\phi$ evaluated at 0;*

2. *Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts*

3. *Matrix A has a right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.*

*Let $f_k$ be the $k^{th}$ component of f and*

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \tag{3.36}$$

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0) \tag{3.37}$$

*Then the local dynamics of system 1 around the x=0 are totally determined by a and b. Particularly,*

1. *$a > 0, b > 0$, when $\phi < 0$ with $||\phi|| \ll 1$, (0,0) is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, (0; 0) is unstable and there exists a negative and locally asymptotically stable equilibrium.*

2. *$a < 0, b < 0$, when $\phi < 0$ with $||\phi|| \ll 1$, (0,0) is unstable; when $0 < \phi \ll 1$, (0; 0) is locally asymptotically stable and there exists exists a positive unstable equilibrium.*

3. $a > 0, b < 0$, *when* $\phi < 0$ *with* $||\phi|| \ll 1$, *(0,0) is unstable and there exists locally asymptotically stable equilibrium; when* $0 < \phi \ll 1$, *(0; 0) stable and positive unstable equilibrium appears.*

4. $a < 0, b > 0$, *when* $\phi$ *changes from negative to positive,* $x$*=0 changes its stability from stable to unstable. Correspondingly, a negative unstable equilibrium becomes locally asymptotically stable*

The algebraic calculation from Theorem 3.4.3 are shown in the working below.

$$\begin{aligned}
\frac{\partial^2 f_2}{\partial x_2 \partial x_2} &= -\frac{2(1-\rho)\psi\mu}{\nu}, & \frac{\partial^2 f_3}{\partial x_2 \partial x_2} &= -\frac{2\rho\psi\mu}{\nu} \\
\frac{\partial^2 f_2}{\partial x_2 \partial x_3} &= -\frac{(1-\rho)(1+\varepsilon)\psi\mu}{\nu}, & \frac{\partial^2 f_3}{\partial x_2 \partial x_3} &= -\frac{\rho\psi\mu(1-\varepsilon)}{\nu} \\
\frac{\partial^2 f_2}{\partial x_2 \partial x_4} &= -\frac{(1-\rho)\psi\mu}{\nu}, & \frac{\partial^2 f_3}{\partial x_2 \partial x_4} &= -\frac{\rho\psi\mu}{\nu} \\
\frac{\partial^2 f_2}{\partial x_3 \partial x_3} &= -\frac{2(1-\rho)\psi\mu\varepsilon}{\nu}, & \frac{\partial^2 f_3}{\partial x_3 \partial x_3} &= -\frac{2\rho\psi\mu\varepsilon}{\nu} \\
\frac{\partial^2 f_2}{\partial x_3 \partial x_4} &= -\frac{(1-\rho)\psi\mu\varepsilon}{\nu} & \frac{\partial^2 f_3}{\partial x_3 \partial x_4} &= -\frac{\rho\psi\,\epsilon}{x_1}
\end{aligned}$$

$$\begin{aligned}
\frac{\partial^2 f_2}{\partial x_2 \psi_c} &= 1-\rho, & \frac{\partial^2 f_3}{\partial x_2 \psi_c} &= \rho \\
\frac{\partial^2 f_2}{\partial x_3 \psi_c} &= (1-\rho)\epsilon, & \frac{\partial^2 f_3}{\partial x_3 \psi_c} &= \rho\epsilon
\end{aligned}$$

**Note:** $\frac{\partial^2 f_k}{\partial x_i \partial x_j} = \frac{\partial^2 f_k}{\partial x_j \partial x_i}$

The rest of the second derivatives that are in (3.36) and (3.37) are all zero. Hence,

$$a = -\frac{((1-q)\varepsilon\,\eta + h_1)v_3 K_8}{\varepsilon\,\eta + \pi + \varepsilon\,\alpha + \mu\,\varepsilon} - \frac{2\,K_4\psi\,\rho\,(K_5 + K_6 + K_7)v_3\mu\,{w_3}^2}{{K_1}^2(\mu+\delta)\nu} \tag{3.38}$$

where

$$
\begin{aligned}
K_1 &= \rho\,(\mu+\alpha)+(\rho q+1-q)\,\eta \\
K_2 &= \pi+(1-\rho)\,(\mu+\beta) \\
K_3 &= \eta\,(\beta+\pi q+\mu q\,(1-\rho))+\rho\beta\,(\mu+\alpha) \\
h_1 &= \beta+\pi+\mu \\
K_4 &= (\eta q-\beta+\alpha)\,\rho+(1-q)\,\eta+h_1 \\
K_5 &= \mu(\epsilon\,\eta+\rho\,\epsilon\,\alpha+\pi-\rho\,\mu\,(1-\epsilon))+\delta(\epsilon\,\eta+\rho\,\epsilon\,\alpha+\pi-\rho\,\mu\,(1-\epsilon)) \\
K_6 &= \mu\,(\delta+\beta+\pi)-\eta\,q\epsilon\,\delta\,(1-\rho) \\
K_7 &= \eta\,q\pi+\beta\,\eta+\beta\,\delta+\mu\,\eta\,q\,(1-\epsilon)\,(1-\rho) \\
K_8 &= 2\,\tfrac{w_3{}^2K_2{}^2(1-\rho)\psi\,\mu}{K_1{}^2\nu}+2\,\tfrac{w_3{}^2K_2(1+\epsilon(1-\rho))\psi\,\mu}{K_1\nu}+2\,\tfrac{w_3{}^2K_2K_3(1-\rho)\psi\,\mu}{K_1{}^2(\mu+\delta)\nu}+2\,\tfrac{w_3{}^2(1-\rho)\psi\,\mu\,\epsilon}{\nu} \\
&\quad +2\,\tfrac{w_3{}^2K_3(1-\rho)\psi\,\mu}{(\mu+\delta)K_1\nu}
\end{aligned}
$$

Since $K_1, K_2, K_3, K_4, K_5, K_6, K_7, K_8$ and $h_2 > 0$ then

$a < 0$

$$
\begin{aligned}
b &= \frac{v_3w_3\,(\pi+\mu+\beta-\rho\,\mu-\rho\,\beta+\epsilon\,\alpha\,\rho+\epsilon\,\rho\,\mu+\epsilon\,\eta\,\rho\,q+\epsilon\,\eta-\epsilon\,\eta\,q)^2}{(\epsilon\,\eta+\pi+\epsilon\,\alpha+\mu\,\epsilon)\,(\alpha\,\rho+\rho\,\mu+\eta\,\rho\,q+(1-q)\,\eta)} \qquad (3.39) \\
b &> 0
\end{aligned}
$$

Using the results in Theorem 3.4.3, the results in (3.38) and (3.39)indicate that there is a forward bifurcation at $\psi = \psi_c$ and there exist at least one locally asymptomatically stable endemic equilibrium when $R_0 > 1$

Using the parameter values in Table 3.3, a transcritical (forward) bifurcation occurs at $\psi = \psi_c = 0.47, (R_0 = 1)$. This implies that there is only one stable equilibrium point if $R_0 < 1$ (disease-free equilibrium) which is unstable when $R > 1$ and a low endemicity when $R_0$ is slightly above one. The result also implies that there can only be one stable endemic equilibrium when $R_0 > 1$. Figure 3.2 (a) and (b).

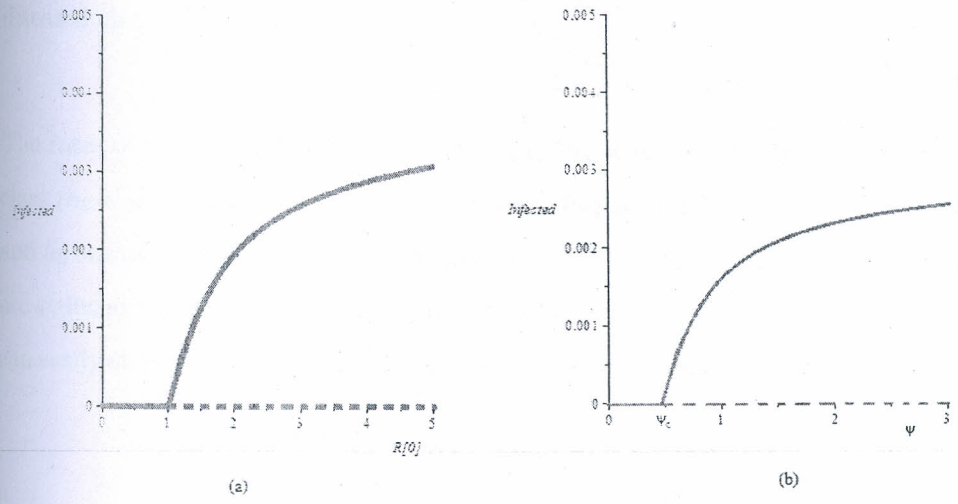


Figure 3.2: Forward bifurcation diagram in (a) plane I,$R_0$ and in (b) plane I,$\psi$

The continuous line represent a stable equilibrium. There are two stable equilibriums (disease free equilibrium for $R_0 < 1$ and an endemic equilibrium for $R_0 > 1$). The dotted line represent the unstable disease free equilibrium. The basic pneumonia model that is analyzed here has two infectious classes (Carriers and Infected). In such models with multi-group infectious classes, forward bifurcation commonly exist (Dushoff et al., 1998). This could be the reason for the existence of forwards bifurcation. A justification of controlling pneumonia by reducing the $R_0$ is indicated by the forward bifurcation results in the numerical analysis. In the presence of a forward bifurcation implies that, a disease can be cleared from the population by just reducing the $R_o$ below 1.

### 3.4.4 Sensitivity analysis of $R_o$

We determine the impact of the parameters on $R_o$ responsible for transmission dynamics of the disease. Consider a case where the the proportion of diseased classes (Infected and Carriers) reduced through increasing their rates of transfer out of the classes the value $R_o$ will reduce. This can be shown easily when we consider the

diseased classes separately.

The rates of transfer out of the infected Class ($h_1 = \mu + \alpha + \eta$) and out of the carrier class ($h_2 = \mu + \pi + \beta$) are used to assess their impact on $R_o$. Increasing the rates $h_1$ and $h_2$ one at a time will ensure that the population of infected and carrier individuals are reduced respectively and hence an effect on $R_o$. As in Sharomi et al.,(2008), we can easily show this by finding the limits of the $R_0$ as $h_1$ and $h_2$ tends to infinity. Thus

$$\lim_{h_1 \to \infty} R_0 = \frac{\varepsilon \rho \psi}{h_2} > 0 \tag{3.40}$$

$$\lim_{h_2 \to \infty} R_0 = \frac{(1-\rho)\psi}{h_1} > 0 \tag{3.41}$$

From the results in (3.40)and (3.41), the disease is cleared from the population if $R_0 \leq 1$ *i.e.* $\varepsilon \rho \psi \leq h_2$ and $(1-\rho)\psi \leq h_1$. These are strategies that can be used to prevent and epidemic of pneumonia. Since $h_1$ and $h_2$ are functions of $\alpha, \eta, \mu$ and $\beta, \mu, \pi$ respectively, it is biologically possible to change the values of $h_1$ and $h_2$ through changing the values of $\eta$ and $\beta$ respectively. We therefore perform a sensitivity analysis on the $R_0$ with respect to $\eta$ and $\beta$.

It can clearly be shown that from (3.17),

$$\lim_{\eta \to \infty} R_0 = \frac{\varepsilon \psi (1 - q + \rho q)}{\pi q + \beta + \mu} > 0 \tag{3.42}$$

and

$$\lim_{\beta \to \infty} R_0 = \frac{\psi (1-\rho)}{\mu + \alpha + \eta} > 0 \tag{3.43}$$

Thus a sufficient effective recovery rate of carriers ($\beta \to \infty$) and infective ($\eta \to \infty$ ) can lead to effective disease control if the RHS of Equations (3.43) and (3.42) are

less than unity. The plot of $R_0$ with respect to $\beta$ and $\eta$ are shown in Figure 3.3.

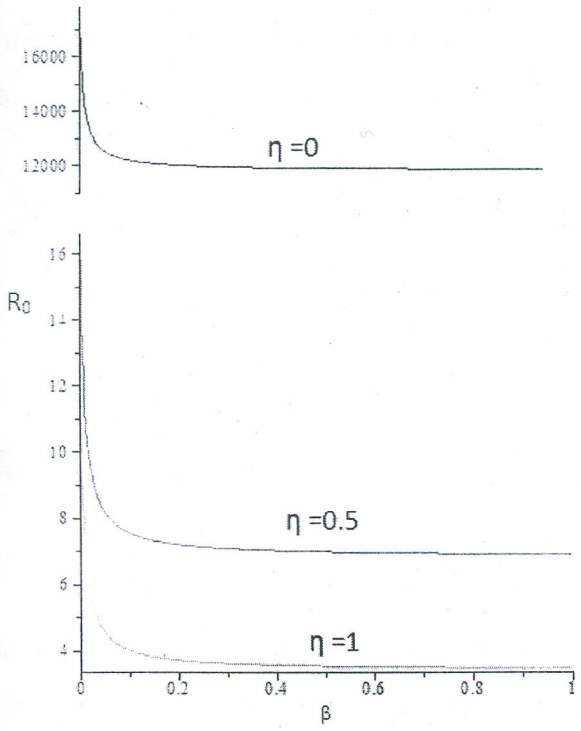


Figure 3.3: Reproduction number as a function of recovery rates.

Strategy focusing only on the recovery of the carriers ($\eta = 0$) may not be significant in controlling the outbreak of pneumonia, despite a significant reduction in $R_0$ from 15,000 to 12,000. On the other hand, employing a strategy that focusses on the recovery of both infected ($\beta > 0$) and carriers ($\eta > 0$) will be significant in controlling the outbreak of pneumonia ($R_0$ reduces from 15,000 to $< 1$). Using the results in (3.43), with $\rho = 0$, that is the recruitment to carrier class is 0, then it makes biological sense that as $t \to \infty$, carrier is always zero because of the death rate (Doura et al., 2000). Therefore the basic reproduction number expressed in (3.17) leads to (3.44) which is a standard $R_o$ for a SIR model.

$$R_{c_0} = \frac{\psi}{\alpha + \mu + \eta} \tag{3.44}$$

We generate more mathematical insight by performing further sensitivity analysis on the recovery rates. Here again we apply the approach used by Sharomi *et al.*(2008)

to carry out the partial derivative of the $R_0$ with respect to the recovery parameters ($\beta$ and $\eta$). giving

$$\left.\begin{array}{l} \frac{\partial R_0}{\partial \eta} = \frac{\psi(\rho\varepsilon+(1-\rho)(1-q)\varepsilon)}{(\mu+\pi+\beta)(\mu+\alpha+\eta)-(1-q)\eta\pi} \\ \\ \quad - \frac{\psi(\rho(\pi+\varepsilon(\mu+\alpha+\eta))+(1-\rho)(\mu+\pi+\beta+(1-q)\eta\varepsilon))(\mu+\pi+\beta-(1-q)\pi)}{((\mu+\pi+\beta)(\mu+\alpha+\eta)-(1-q)\eta\pi)^2} \end{array}\right\} \quad (3.45)$$

and,

$$\left.\begin{array}{l} \frac{\partial R_0}{\partial \beta} = \frac{\psi(1-\rho)}{(\mu+\pi+\beta)(\mu+\alpha+\eta)-(1-q)\eta\pi} \\ \\ \quad - \frac{\psi(\rho(\pi+\varepsilon(\mu+\alpha+\eta))+(1-\rho)(\mu+\pi+\beta+(1-q)\eta\varepsilon))(\mu+\alpha+\eta)}{((\mu+\pi+\beta)(\mu+\alpha+\eta)-(1-q)\eta\pi)^2} \end{array}\right\} \quad (3.46)$$

From (3.45), consider a case where $\beta = 0$, then $R_0$ is a decreasing function of $\eta$ (i.e $\frac{\partial R_0}{\partial \beta} < 0$) $D_1 < D_2$. Similarly from (3.46), for ($\eta = 0$ then $R_0$ is a decreasing function of $\eta$ (i.e $\frac{\partial R_0}{\partial \eta} < 0$) $D_3 < D_4$

where,

$$D_1 = \psi(\rho\varepsilon + (1-\rho)(1-q)\varepsilon)$$

$$D_2 = \frac{\psi(\rho(\pi+\varepsilon(\mu+\alpha+\eta)) + (1-\rho)(\mu+\pi+(1-q)\eta\varepsilon))(\mu+\pi-(1-q)\pi)}{(\mu+\pi)(\mu+\alpha+\eta)-(1-q)\eta\Pi}$$

$$D_3 = (\psi(1-\rho))(\mu+\pi+\beta)(\mu+\alpha+\eta) - (1-q)\eta\pi$$

$$D_4 = \frac{\psi(\rho(\pi+\varepsilon(\mu+\alpha+\eta)) + (1-\rho)(\mu+\pi+\beta+(1-q)\eta\varepsilon))(\mu+\alpha+\eta)}{(\mu+\pi+\beta)(\mu+\alpha+\eta)-(1-q)\eta\pi}$$

The following proposition can therefore be used to summarize the above conditions.

**Proposition 3.4.4** *The recovery strategy of the infective individuals will be significant on reducing pneumonia if $D_1 < D_2$ , otherwise insignificant.*

**Proposition 3.4.5** *The recovery strategy of the carrier individuals will be significant if $D_3 < D_4$ , otherwise insignificant.*

If the condition in $D_1 < D_2$ and $D_3 < D_4$ are not met then the recovery strategy will not have any significant impact of reducing pneumonia burden in the population.

## 3.5 Numerical Simulations

To observe the transmission dynamics of pneumonia model over time, numerical simulations are done using MAPLE 14.0 (a mathematical simulation package). Based on the fact that pneumonia has adverse effect on the children under five year of age (World Health Organization, 2011; Kllander et al., 2008) due to their law immune system, the parameters that will be used in the numerical simulation will be based on the data for children under five year of age. Some values assigned to the parameters have been derived from epidemiological literature while other parameters have been estimated within the values where they make biological sense.

Table 3.3: Parameter Value used in the basic pneumonia model

| Parameter | Value | Source |
|---|---|---|
| $\nu$ | $\mu N_0$ | (Doura et al., 2000) |
| $\kappa$ | 1-10 per day | Estimated |
| $\mathcal{P}$ | 0.89 to 0.99 | (Doura et al., 2000) |
| $\psi$ | $\kappa\mathcal{P}$ | Expressed as in (3.2) |
| $\epsilon$ | 0.001124 | (Doura et al., 2000) |
| $\rho$ | 0.338 | (Kateete et al., 2012; Kimura et al., 1984) |
| $\pi$ | 0.00274 to 0.01096 per day | (Doura et al., 2000) |
| $\eta$ | 0.0238 to 0.0476 per day | (Thadani, 2011) |
| $q$ | 0.5 to 1 | (Doura et al., 2000) |
| $\alpha$ | 0.33 | Estimated |
| $\delta$ | 0.2 | Estimated |
| $\mu$ | 0.0002 per day | (World Health Organization, 2010) |
| $\beta$ | 0.0115 | (Hill et al., 2008) |

### 3.5.1 Numerical simulation of the endemic equilibrium points.

We carry out numerical simulations of the basic pneumonia model represented in (3.1) using a hypothetical population of size 100. We will vary key parameters to investigate the efficient way of controlling pneumonia. Using the parameter values given in Table 3.3, we study the dynamical behavior of the system. The equilibrium values are computed as follows.

$S^e = 24.41243257$

$C^e = 0.4522552372$

$I^e = 4.549013989 \times 10^{-2}$

$R^e = 3.109122565 \times 10^{-2}$

The corresponding eigenvalues of the jacobian matrix of the endemic equilibrium are:

$\lambda_{1,2}$ $-2.094517752 \times 10^{-3} \pm 7.155467879 \times 10^{-3}i$

$\lambda_3$ $-6.661627616 \times 10^{-2}$

$\lambda_4$ $-0.2001328655 \times 10^{-1}$

Since all the real parts of the eigenvalues are negative, it confirms that the endemic equilibrium is locally asymptotically stable for the parameter values given in Table 3.3. Using (3.17), the numerical solution for the basic reproduction number is approximately 4 ($R_0 = 4.096273473$), indicating that when one infected individual is introduced into a purely susceptible population, there will be 10 secondary newly infected individuals. This indicates that there is a unique positive endemic equilibrium. Picking different initial condition of the infected individuals $I(0)$=1, 10, 20 and 30, respectively and plot their solution curves using phase plane portrait of I vs S (Figure 3.4, we clearly see that all the four orbits converge to the equilibriun, showing global asymptotic stability of the endemic equilibrium.

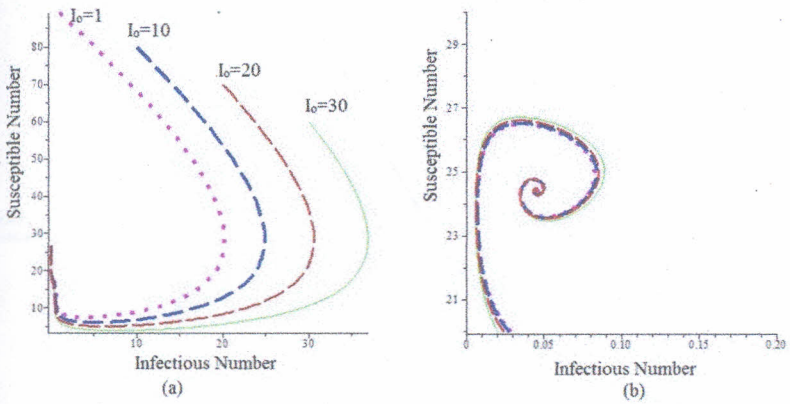


Figure 3.4: The phase plane portrait of S vs I for 3.1. The four curves correspond to the initial conditions $I_0$= 1, 10, 20 and 30 respectively. They all converge at $I^e = 4.549013989$ and $S^e = 24.41243257$ as in (b) when the plot is magnified

### 3.5.2 Effect of the carrier-infected interaction

Carriers play a very important role in disease transmission dynamic. Their presence my hinder the disease eradication since in most cases, such individual are not aware of their status and continue to interact with others in a normal way, hence unknowingly propagate the disease incidence. Figure 3.5 indicates the dynamics of pneumonia when the interaction between the Carrier class and the infected class is reduced towards zero.

Here, we reduce the interaction between the carrier and the infected classes. Two parameters are varied such that: $q$ is increased while $\pi$ is decreased. Increasing the value of $q$ reduces the function $1 - q$ hence reducing the proportion of infected individuals who recover and become carriers again. Reducing the value of $\pi$ ensures that the proportion of carriers who eventually get infected is reduced. The results shown in Figure 3.5 indicates that the strategy of reducing the interaction between the carrier and the infected has an effect on the prevalence rate of pneumonia within

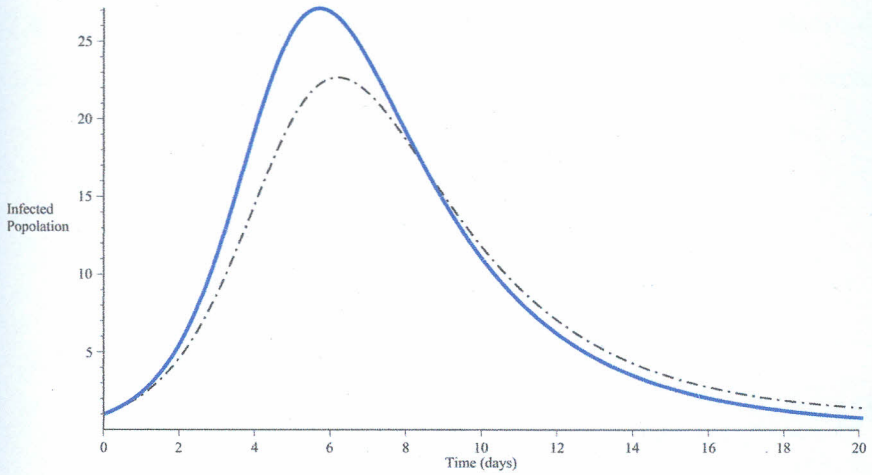


Figure 3.5: Effect of reducing the interaction between carrier and infected classes (from $\pi$=0.005, q=0.75 to $\pi$ =0 and q=0.999)

the first 10 days while in the long run, it reduces the infected population. A strategy to reduce the number of infected would be to treat the infected within the 6 days.

Using MALPLE 14, data for the infected population in both the cases (dotted line and continuous line in Figure 3.5 was generated and analyzes to check if there is any significant difference in the two populations. Table 3.4 shows the results of the statistical analysis.

Since the P-value=$2.1344 \times 10^{-15}$ for the t-test for mean difference is less than 0.01, we conclude that there is a strong significant different between the two infected populations. This means that there will be a significant reduction on the proportion of the infected individuals when efforts are spent on reducing the the carrier-infected interaction.

Table 3.4: t-Test: Paired Two Sample for Means(testing for the significant difference between infected populations when the values of $\pi$ $\beta$ and q are varied respectively)

| Statistics | Infected Population ($\pi$ =0.005, q=0.75) | Infected population ($\pi$ =0, q=0.999) |
|---|---|---|
| Mean | 2.486300321 | 2.170599263 |
| Variance | 20.90683033 | 20.72202111 |
| Observations | 100 | 100 |
| Hypothesis | Mean Difference=0 | |
| df | 99 | |
| t Statistics | 9.408577558 | |
| P- Value | $2.1344 \times 10^{-15}$ | |
| t Critical | 1.9842169 | |



### 3.5.3 Effect of the "increase in Infected recovery rate and decrease of carrier-infected interaction"

Increasing the recovery rate of the infected individual and reducing the carrier-infected interaction will increase the rate of transfer of individuals from the infected class to the recovered class. This reduces the infected population at a faster. Based on the analysis of this model, we found out that there is a possibility of reducing the incidence of pneumonia infection. We suggest three possible control measures: Reducing the rate of of contact of individuals, reducing the interaction transfer rate between the carriers and the infected classes and increasing the recovery rate of the infected individuals. All the three suggested control measures ensures that the basic reproduction number is reduced. In chapter 4, we shall discuss the effect of using vaccination and treatment as control measures.

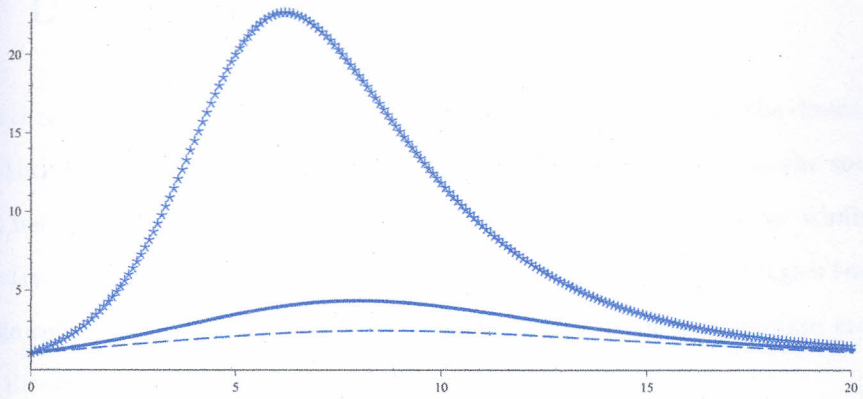


Figure 3.6: Effect of increasing considering recovery rate and decreasing the interaction between carrier and infected classes. The stared line ($\pi$=0.005, q= 0.75, $\eta$=0.03), Thick line ($\pi$=0.005, q= 0.75, $\eta$=0.6), dashed line ($\pi$=0, q= 0.999, $\eta$=0.6)

### 3.5.4 Effect of carrier proportion

We also Simulate the effect of different proportion of carriers on transmission by considering different initial proportion of carriers and different rate of transfer leading to increase in carrier proportion in the population.

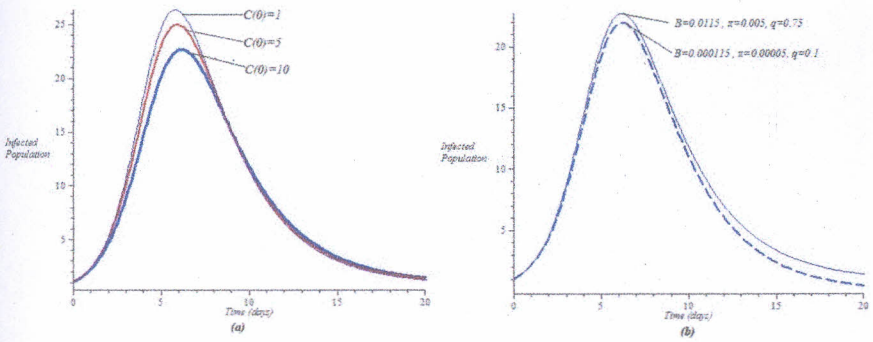


Figure 3.7: Dynamics considering recovery rate of the infected and carrier-infected transfer rates. The continuous line is plotted when $\eta = 0.03$,$\pi = 0.005$ and $q = 0.75$ while The dotted line is plotted when $\eta = 0.6$, $\pi = 0$ and $q = 0.999$,

## 3.6 Discussion

Where there is existence of the risk factors of pneumonia infections, the disease continues to thrive, this will have a negative social and economic impact to the society. An urgent need to promptly detect the symptoms, diagnosis correctly an administer effective treatment is needed. We suggest possible disease control strategies that ensure possible reduction or guard against incidences of infections or complete eradication of the disease

# Chapter 4

# A MODEL OF PNEUMONIA WITH TREATMENT AND VACCINATION

## 4.1 Introduction

This chapter describes a model that considers a transmission dynamic of pneumonia in a population divided into six compartments according their disease status viz: Susceptible, Vaccinated, Infected, Carriers, Treatment and Recovered. A detailed biological explanation of transmission rates of the disease is discussed in the next section. The successive sections describe the analysis of the model to determine the threshold parameters, equilibrium points and their stabilities and to assess the effect of treatment and vaccination on optimal conditions necessary for controlling pneumonia. Finally a probabilistic simulation is used to estimate the probability distribution of the basic reproduction number by applying the Monte Carlo simulation approach.

## 4.2 Model Description and Formulation

The susceptible population can be increased by new recruitment of individuals through either birth or immigration at a constant rate $\nu$. We assume that every recruitment into the population under study joins the susceptible class. A proportion, $\phi$ of susceptible moves to the vaccinated class when they receive a vaccine against the disease. The vaccine is expected to protect an individual from getting infected by the bacteria, however the probability that the vaccine will wane out is $\omega$ (Nuorti & Whitney, 2010) (and therefore $1-\omega$ is vaccine efficacy). The susceptible can be infected by either carriers or by symptomatically infected individual with a force of infection $\lambda$. The

current 23-valent vaccine, containing 25 g each of 23 purified capsular polysaccharide (CP) antigens can only protect against 23 invasive serotype of streptococcus (Butler et al., 1996) out of the 90 serotype (Henrichsen, 1995). This means that vaccinated individuals can still be susceptible to the uncovered serotype and can get infected with a force of infection $\lambda_v = \epsilon\lambda$, where $\epsilon$ is the proportion of the serotype not covered in the vaccine. A newly infected individual can either become a carrier with a probability $\rho$ or show disease symptoms with a probability $(1 - \rho)$. The carriers can develop disease symptoms and become symptomatically infectious (McKenzie, 1999) at a rate $\pi$ or recover to gain immunity against the bacteria at an average rate $\beta$. Let the uptake rate of therapeutic treatment by the infected be $\xi$ while the rate of transfer from treatment class is denoted by $\vartheta$. The transfer out of the treatment class is due to movement to recovery class if the treatment is effective or movement to infected class if the treatment is ineffective. The proportion of individuals for whom treatment is effective is denoted by $\tau$. When treatment is applied, we assume that bacteria will be cleared and therefore the rate of transfer from the symptomatically infected class to the carrier class is negligible. The infected individuals on the other hand can recover at a percapita rate of $\eta$ or die from the disease at a rate $\alpha$. The rate of losing the immunity is denoted by $\delta$ so that the recovered individual move to the susceptible again. We denote the natural percapita mortality rate by $\mu$. A summary of the disease parameters are shown in Table 4.1. Using the variables and parameter described here, we generate the systems of differential equations for the model as in (4.1).

Table 4.1: Description of parameter used in the pneumonia model with control strategies

| Parameter | Description |
|---|---|
| $\nu$ | Recruitment rate into the susceptible class |
| $\lambda$ | Force of infection |
| $\rho$ | Probability of a newly infected individual being a Carrier |
| $\pi$ | Rate at which Carriers become symptomatically infectious |
| $\eta$ | Rate of recovery from the symptomatically infection |
| $\alpha$ | Per capita disease-induced death rate |
| $\delta$ | Per capita rate of loss of immunity |
| $\mu$ | Per capita birth rate |
| $\beta$ | Recovery rate of carriers and gaining partial immunity |
| $\xi$ | Rate of joining the treated class |
| $\tau$ | Treatment efficacy |
| $\vartheta$ | Transfer rate out of the treatment class |
| $\phi$ | Proportion of the susceptible who get vaccinated |
| $\omega$ | Rate at which the vaccine wanes |
| $\epsilon$ | proportion of the serotype not covered in the vaccine |

$$\left.\begin{aligned}
\frac{dS(t)}{dt} &= \nu + \delta R(t) + \omega V(t) - (\lambda + \phi + \mu)S(t) \\
\frac{dV(t)}{dt} &= \phi S(t) - (\mu + \omega + \epsilon\lambda)V(t) \\
\frac{dI(t)}{dt} &= (1-\rho)\lambda S(t) + (1-\rho)\epsilon\lambda V(t) + \pi C(t) + (1-\tau)\vartheta T(t) - (\mu + \alpha + \xi)I(t) \\
\frac{dT(t)}{dt} &= \xi I(t) - (\mu + \vartheta)T(t) \\
\frac{dC(t)}{dt} &= \rho\lambda S(t) + \rho\epsilon\lambda V(t) - (\mu + \pi + \beta)C(t) \\
\frac{dR(t)}{dt} &= \tau\vartheta T(t) + \beta C(t) - (\mu + \delta)R(t)
\end{aligned}\right\} \tag{4.1}$$

The total population at time t is expressed as

$$N(t) = S(t) + I(t) + C(t) + V(t) + T(t) + R(t) \tag{4.2}$$

The rate of change of the population size can be determined by adding all the equations in (4.1) resulting to;

$$\frac{dN(t)}{dt} = \nu - \mu N(t) - \alpha I(t) \tag{4.3}$$

The schematic diagram representing the systems of equations in (4.1) is shown in Figure 4.1

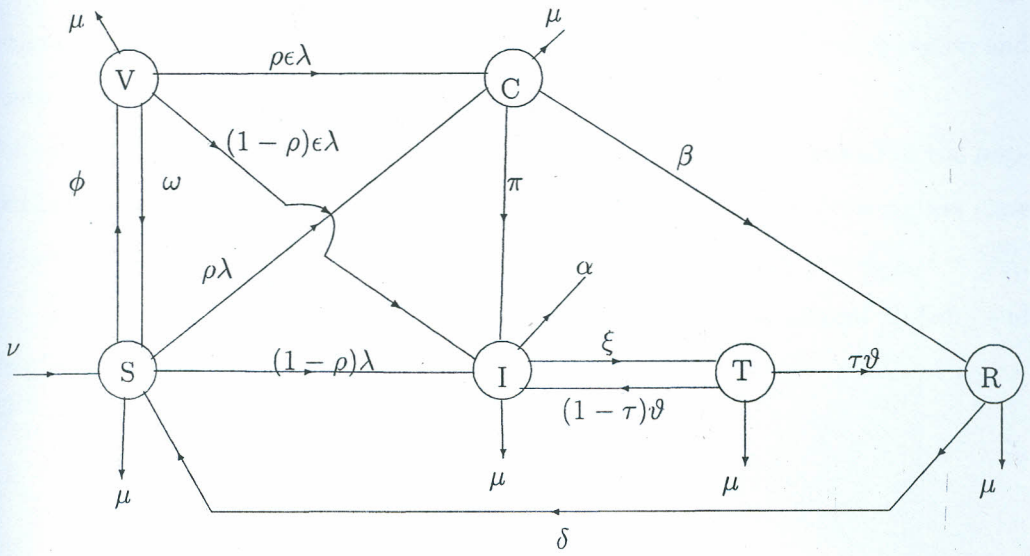


Figure 4.1: Compartmental model for pneumonia transmission with control strategies

## 4.3 Analysis of the pneumonia model with treatment and vaccination

The model for pneumonia transmission with treatment and vaccination was analyzed to determine the basic reproduction number and other threshold parameters.

For biological reasons, we assume that all state variable are more than or equal to zero for any time t i.e. System (4.1) has its initial conditions given by:

$S(0) = S_0 \geq 0 \quad V(0) = V_0 \geq 0 \quad I(0) = I_0 \geq 0 \quad C(0) = C_0 \geq 0$

$T(0) = T_0 \geq 0 \quad R(0) = R_0 = 0 \quad N(0) = N_0 \geq 0$

From (4.2), the boundedness of solutions for (4.1) can easily be proven. Since $0 \leq N(t) = S(t) + I(t) + C(t) + V(t) + T(t) + R(t) \leq \frac{\nu}{\mu}$, then any variable of $\{N(t), S(t), I(t), C(t), V(t), T(t), R(t)\}$ lies in the range $(0, \frac{\nu}{\mu})$ .

System (4.1) is then studied in a suitable region:

$$\Omega = \{(S, V, I, C, T, R) \in \mathbb{R}^6_+ : 0 \leq N(t) \leq \tfrac{\nu}{\mu}\}.$$

Thus $\Omega$ is positively invariant with respect to (4.1)and it is sufficient to consider solutions starting in $\Omega$ to remain in $\Omega$. Therefore $\Omega$ is biologically feasible region and hence model (4.1) is mathematically posed.

For easier computation and analysis of (4.1), we use proportions instead of the population sizes. The proportion of each variable can be obtained by dividing the class population sizes by the total population to get: $s = \frac{S(t)}{N(t)}$, $v = \frac{V(t)}{N(t)}$, $i = \frac{I(t)}{N(t)}$, $c = \frac{C(t)}{N(t)}$, $f = \frac{T(t)}{N(t)}$ and $r = \frac{R(t)}{N(t)}$. Then, by differentiating fractions with respect to time and simplifying, we have

$$\begin{aligned}
\tfrac{ds}{dt} &= \tfrac{d}{dt}\tfrac{S}{N} \\
&= \tfrac{N(\frac{dS}{dt}) - S(\frac{dN}{dt})}{N^2} \\
&= \frac{1}{N}[\frac{dS}{dt} - s\frac{dN}{dt}] \\
&= \tfrac{1}{N}[\nu + \delta R + \omega V - (\lambda + \phi + \mu)S - s(\nu - \mu N - \alpha I)] \\
&= \tfrac{\nu}{N} + \delta r + \omega v - (\lambda + \phi + \mu)s - s(\tfrac{\nu}{N} - \mu - \alpha i) \\
&= \tfrac{\nu}{N}(1 - s) + \delta r + \omega v + \alpha i s - (\psi i + \varepsilon\psi c + \phi)s
\end{aligned}$$

The rest of the rates of change of proportion are determined in the same way. Therefore (4.1) can be re-written as;

$$\left.\begin{aligned}
\frac{ds(t)}{dt} &= \frac{\nu}{N}(1-s) + \delta r + \omega v + \alpha i s - (\psi i + \varepsilon\psi c + \phi)s \\
\frac{dv(t)}{dt} &= \phi s + \alpha v i - (\omega + \epsilon\psi i + \varepsilon\epsilon\psi c + \frac{\nu}{N})v \\
\frac{di(t)}{dt} &= (1-\rho)(\psi i + \psi\epsilon c)(s + \epsilon v) + \pi c + (1-\tau)\vartheta f - (\alpha + \xi + \frac{\nu}{N})i + \alpha i^2 \\
\frac{df}{dt} &= \xi i - (\vartheta + \frac{\nu}{N})f + \alpha i t \\
\frac{dc}{dt} &= \rho(\psi i + \psi\epsilon c)(s + \epsilon v) - (\pi + \beta + \frac{\nu}{N})c + \alpha i c \\
\frac{dr}{dt} &= \tau\vartheta f + \beta c - (\frac{\nu}{N} + \delta)r + \alpha i r
\end{aligned}\right\} \quad (4.4)$$

Using (4.3) at steady state i.e. $\frac{\nu}{N} = \mu + \alpha i$ and an expression $s+v+i+c+t+r = 1$, we substitute $s = 1-r-v-i-c-t$ into each of the equations in (4.4). This reduces the System (4.1) to a five-dimensional system shown in (4.5);

$$\left.\begin{aligned}
\frac{dv}{dt} &= \phi(1-r-v-i-c-f) + \alpha v i - (\omega + \epsilon\psi i + \varepsilon\epsilon\psi c + \mu + \alpha i)v \\
\frac{di}{dt} &= (1-\rho)(\psi i + \psi\varepsilon c)((1-r-v-i-c-f) + \epsilon v) + \pi c + (1-\tau)\vartheta f \\
&-(\alpha + \xi + \mu + \alpha i)i + \alpha i^2 \\
\frac{df}{dt} &= \xi i - (\vartheta + \mu + \alpha i)t + \alpha i f \\
\frac{dc}{dt} &= \rho(\psi i + \psi\varepsilon c)((1-r-v-i-c-f) + \epsilon v) - (\pi + \beta + \mu + \alpha i)c + \alpha i c \\
\frac{dr}{dt} &= \tau\vartheta f + \beta c - (\mu + \alpha i + \delta)r + \alpha i r
\end{aligned}\right\} \quad (4.5)$$

System (4.5) can now be studied in $\Gamma$, where

$\Gamma = \{(v, c, i, f, r) \in \mathbb{R}^5_+ : 0 \leq v, 0 \leq c, 0 \leq i, 0 \leq f, 0 \leq r, v + c + i + f + r \leq 1\}$

All the solutions of system (4.5) are positively invariant in $\Gamma$.

### 4.3.1 Basic reproduction number (with treatment and vaccination strategies)

To determine the basic reproduction number of (4.5) the next generation operator method. Re-arranging the equations starting with the diseased classes, we have

$$\left.\begin{aligned}
&\tfrac{di}{dt} = (1-\rho)(\psi i + \psi\varepsilon c)((1-r-v-i-c-f)+\epsilon v) + \pi c + (1-\tau)\vartheta f \\
&-(\alpha+\xi+\tfrac{\nu}{N})i + \alpha i^2 \\
&\tfrac{dc}{dt} = \rho(\psi i + \psi\varepsilon c)((1-r-v-i-c-f)+\epsilon v) - (\pi+\beta+\tfrac{\nu}{N})c + \alpha i c \\
&\tfrac{df}{dt} = \xi i - (\vartheta+\tfrac{\nu}{N})f + \alpha i f \\
&\tfrac{dN}{dt} = (\tfrac{\nu}{N} - \mu - \alpha i)N \\
&\tfrac{dr}{dt} = \tau\vartheta f + \beta c - (\tfrac{\nu}{N}+\delta)r + \alpha i r \\
&\tfrac{dv}{dt} = \phi(1-r-v-i-c-f) + \alpha v i - (\omega + \epsilon\psi i + \varepsilon\epsilon\psi c + \tfrac{\nu}{N})v
\end{aligned}\right\} \quad (4.6)$$

Let $\mathcal{F}_{]_i}$ be the rate of appearance of new infections into the compartment and $\mathcal{V}_{]_i} = \mathcal{V}_{]_i}^- - \mathcal{V}_{]_i}^+$ where $\mathcal{V}_{]_i}^+$ is the rate of transfer of individuals into the particular compartments, $\mathcal{V}_i^-$ is the rates of transfer out of the compartment . Then we compute $F_c$ and $V_c$ which are evaluated by finding the partial derivative at disease free equilibrium of $\mathcal{F}_{]_i}$ and $\mathcal{V}_{]_i}$ respectively. That is;

$$V_c = \begin{bmatrix} \alpha+\xi+\mu & -\pi & -(1-\tau)\vartheta & 0 \\ 0 & \pi+\beta+\mu & 0 & 0 \\ \xi & 0 & -\vartheta-\mu & 0 \\ -\frac{\alpha\nu}{\mu} & 0 & 0 & -\mu \end{bmatrix}$$

and

$$F_c = \begin{bmatrix} \psi(1-\rho)(1-\frac{\phi}{\phi+\omega+\mu}+\frac{\epsilon\phi}{\phi+\omega+\mu}) & \psi(1-\rho)(\varepsilon+\frac{\varepsilon\epsilon\phi}{\phi+\omega+\mu}-\frac{\varepsilon\phi}{\phi+\omega+\mu}) & 0 & 0 \\ \rho\psi(1-\frac{\phi}{\phi+\omega+\mu}+\frac{\epsilon\phi}{\phi+\omega+\mu}) & \rho\psi(\varepsilon+\frac{\varepsilon\epsilon\phi}{\phi-\omega+\mu}-\frac{\varepsilon\phi}{\phi+\omega+\mu}) & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

We now obtain the basic reproduction number $R_0$ by defining the spectral radius (dominant eigenvalue) of the matrix $F_cV_c^{-1}$ as;

$$R_\phi = \frac{\psi(\mu+\epsilon\phi+\omega)((\mu+\vartheta)(\mu-\mu\rho+\pi+\beta-\rho\beta)+\rho\varepsilon\vartheta(\alpha+\mu+\xi\tau)+\mu(\alpha+\mu+\xi))}{\vartheta(\alpha+\mu+\xi\tau)+\mu(\alpha+\mu+\xi)(\phi+\omega+\mu)(\pi+\beta+\mu)} \quad (4.7)$$

$$R_\phi = \left[\frac{\mu+\epsilon\phi+\omega}{\phi+\omega+\mu}\right]\left[\frac{\psi[(\mu+\vartheta)\{(1-\rho)(\pi+\beta+\mu)+\rho\pi\}+\rho\varepsilon[\vartheta(\alpha+\mu+\xi\tau)+\mu(\alpha+\mu+\xi)]]}{[\vartheta(\alpha+\mu+\xi\tau)+\mu(\alpha+\mu+\xi)](\pi+\beta+\mu)}\right] \tag{4.8}$$

**Effect of vaccination on Basic reproduction number**

Assume that $\tau = 1$ (the treatment is 100% effective), and define $h_{1c} = \alpha + \mu + \xi$ as transfer rates out of $I$ class and $h_{2c} = \pi + \beta + \mu$ as transfer rates out of $C$ class. Then $h_1$ and $h_2$ have the same biological meaning as defined in Section 3.3.2.

The first term of (4.8), $\left[\frac{\mu+\epsilon\phi+\omega}{\phi+\omega+\mu}\right]$ corresponds to the vaccination parameter and can be expressed further as

$$\left[\frac{\mu+\epsilon\phi+\omega}{\phi+\omega+\mu}\right] = \left[1 - \frac{(1-\epsilon)\phi}{\phi+\omega+\mu}\right]$$

**Lemma 4.3.1** $0 \leq \dfrac{(1-\epsilon)\phi}{\phi+\omega+\mu} \leq 1$

**Proof** Consider the first equation in system (4.5)

$\frac{dv}{dt} = \phi(1-r-v-i-c-f) + \alpha vi - (\omega + \epsilon\psi i + \epsilon\varepsilon\psi c + \mu + \alpha i)v$

$\frac{dv}{dt} = \phi(1-r-v-i-c-f) - (\omega + \epsilon\psi i + \epsilon\varepsilon\psi c + \mu)v$

$\frac{dv}{dt} \leq \phi(1-v) - (\omega+\mu)v$

$\frac{dv}{dt} \leq \phi - (\phi+\omega+\mu)v$

solving for $v(t)$ gives

$$v(t) \leq \frac{\phi}{\phi+\omega+\mu} + v_0 e^{-(\phi+\omega+\mu)t} \tag{4.9}$$

As $t \to \infty$ we obtain $0 \leq v(t) \leq 1$.

hence $0 \leq \dfrac{\phi}{\phi+\omega+\mu} \leq 1$. Since $0 \leq \epsilon \leq 1$ then

$$\left[1 - \frac{(1-\epsilon)\phi}{\phi+\omega+\mu}\right] < 1 \tag{4.10}$$

The second term in (4.8) corresponds to $R_o$ computed in Section 3.3.2 as shown below.

$$\left[\frac{\psi[(\mu+\vartheta)\{(1-\rho)(\pi+\beta+\mu)+\rho\pi\}+\rho\varepsilon[\vartheta(\alpha+\mu+\xi\tau)+\mu(\alpha+\mu+\xi)]]}{[\vartheta(\alpha+\mu+\xi)+\mu(\alpha+\mu+\xi)](\pi+\beta+\mu)}\right]$$

$$= \left[\frac{\psi[(\mu+\vartheta)\{(1-\rho)(\pi+\beta+\mu)+\rho\pi\}+\rho\varepsilon[(\mu+\vartheta)(\alpha+\mu+\xi)]]}{(\mu+\vartheta)(\alpha+\mu+\xi)(\pi+\beta+\mu)}\right]$$

$$= \left[\frac{\psi[\{(1-\rho)(\pi+\beta+\mu)+\rho\pi\}+\rho\varepsilon(\alpha+\mu+\xi)]}{(\alpha+\mu+\xi)(\pi+\beta+\mu)}\right]$$

$$\left[\frac{\psi[\{(1-\rho)h_{2c}+\rho\pi\}+\rho\varepsilon h_{1c}]}{h_{1c}h_{2c}}\right] \tag{4.11}$$

Equation (4.11) is equivalent to the basic reproduction number of pneumonia transmission when no control strategies used shown in (3.17) with $q = 1$, hence we have $R_\phi$ expressed as;

$$R_\phi = \left[1 - \frac{(1-\epsilon)\phi}{\phi+\omega+\mu}\right] R_o \tag{4.12}$$

From (4.10) and (4.12), it implies that $R_\phi \leq R_0$

when $\phi = 0$ (implying that there is no vaccination), then $R_\phi = R_0$. The introduction of vaccination implies that $R_\phi \leq R_0$, and consequently if $R_0 < 1$, then $R_\phi < 1$ for $\phi > 0$.

**Critical value for the proportion of strains to be covered in the vaccine**

Since $\phi \geq 0$ and $0 \leq \epsilon \leq 1$, then from (4.12) we can deduce that:

$$\left[1 - \frac{(1-\epsilon)\phi}{\phi+\omega+\mu}\right] R_o = 1 \tag{4.13}$$

making $\epsilon$ the subject, we have

$$\epsilon^* = \frac{1}{R_o} + \left(\frac{\omega+\mu}{\phi}\right)\left(\frac{1}{R_o} - 1\right) \tag{4.14}$$

We define $\epsilon^{'} = 1 - \epsilon^*$ as the critical value for the proportion of strains that need to be covered in the vaccine below which the disease will invade.

Furthermore, from (4.12), we set $R_\phi = 1$ and solving for $\phi$ gives the threshold vaccination rate i.e.

$$\phi^* = \frac{(R_0 - 1)(\omega + \mu)}{1 - \epsilon R_0} \tag{4.15}$$

### Treatment Effect on Basic reproduction number

Let $\breve{R}_\tau = \left[\frac{\mu+\epsilon\phi+\omega}{\phi+\omega+\mu}\right]\left[\frac{\psi[(\mu+\vartheta)\{(1-\rho)(\pi+\beta+\mu)+\rho\pi\}+\rho\varepsilon[\vartheta(\alpha+\mu+\xi\tau)+\mu(\alpha+\mu+\xi)]]}{[\vartheta(\alpha+\mu+\xi\tau)+\mu(\alpha+\mu+\xi)](\pi+\beta+\mu)}\right]$

for $\phi = 0$ (considering treatment only as a control strategy), then ,

$$R_\tau = \frac{\psi}{(\pi+\beta+\mu)}\left[\frac{(\mu+\vartheta)\{(1-\rho)(\pi+\beta+\mu)+\rho\pi\}+\rho\varepsilon\{\vartheta(\alpha+\mu+\xi\tau)+\mu(\alpha+\mu+\xi)\}}{[\vartheta(\alpha+\mu+\xi\tau)+\mu(\alpha+\mu+\xi)]}\right] \tag{4.16}$$

or

$$R_\tau = \frac{\psi}{(\pi+\beta+\mu)}\left[\frac{(\mu+\vartheta)\{(1-\rho)(\pi+\beta+\mu)+\rho\pi\}}{\vartheta(\alpha+\mu+\xi\tau)+\mu(\alpha+\mu+\xi)} + \rho\varepsilon\right]$$

differentiating $R_\tau$ with respect to $\tau$ yields

$$-\frac{\psi\,(\mu+\vartheta)(\mu-\mu\,\rho+\pi+\beta-\rho\,\beta)\vartheta\,\xi}{(\pi+\beta+\mu)(\vartheta\,(\alpha+\mu+\xi\,\tau)+\mu\,(\alpha+\xi+\mu))^2}$$

Then $R_\tau$ is a decreasing function with respect to $\tau$ implying that any increase in the treatment efficacy is a significant strategy for controlling the disease.

### 4.3.2 Existence of Equilibrium points

There are two equilibrium points of (4.5) namely; disease free equilibrium $E_{0c}$ and endemic equilibrium $E_c^*$. The disease free equilibrium can occur when there is absence of the disease in the population i.e when $i = c = 0$ while endemic equilibrium can occur in the presence of the disease i.e. when not all $i$ and $c$ are qual to zero. At the equilibrium point the populations does not change with time hence, we obtain the equilibrium point $(s^*, v^*, i^*, c^*, t^*, r^*)$ of the model (4.6), by solving,

$$\frac{dv}{dt} = \frac{di}{dt} = \frac{df}{dt} = \frac{dc}{dt} = \frac{dr}{dt} = \frac{dN}{dt} = 0 \tag{4.17}$$

i.e.

$$\left.\begin{aligned}
\phi(1-r-v-i-c-f) + \alpha v i - (\omega + \epsilon\psi i + \varepsilon\epsilon\psi c + \tfrac{\nu}{N})v = 0 \\
(1-\rho)(\psi i + \psi\varepsilon c)((1-r-v-i-c-f) + \epsilon v) + \pi c + (1-\tau)\vartheta f - \\
(\alpha + \xi + \tfrac{\nu}{N})i + \alpha i^2 = 0 \\
\xi i - (\vartheta + \tfrac{\nu}{N})t + \alpha i f = 0 \\
\rho(\psi i + \psi\varepsilon c)((1-r-v-i-c-f) + \epsilon v) - (\pi + \beta + \tfrac{\nu}{N})c + \alpha i c = 0 \\
\tau\vartheta f + \beta c - (\tfrac{\nu}{N} + \delta)r + \alpha i r = 0 \\
(\tfrac{\nu}{N} - \mu - \alpha i)N = 0
\end{aligned}\right\} \tag{4.18}$$

Solving for the variables in terms of $i^*$ and $c^*$ we obtain the solutions in (4.19)

$$\left.\begin{aligned}
N^* &= \tfrac{\nu}{\mu+\alpha i^*} \\
f^* &= \tfrac{\xi i^*}{\vartheta+\mu} \\
r^* &= \tfrac{\tau\vartheta\xi i^* + \beta c^*(\vartheta+\mu)}{(\vartheta+\mu)(\mu+\delta)} \\
v^* &= \tfrac{\phi((\vartheta+\mu)(\mu+\delta)(1-i^*-c^*) - i\xi(\delta+\mu+\tau\vartheta) - \beta c^*(\vartheta+\mu))}{(\vartheta+\mu)(\mu+\delta)(\mu+\phi+\epsilon\varepsilon\psi c^* + \epsilon\psi i^* + \omega)} \\
s^* &= \tfrac{(\mu+\omega+\epsilon\psi i^* + \epsilon\varepsilon\psi c^*)((\vartheta+\mu)(\mu+\delta)(1-i-c)) - i^*\xi(\delta+\mu+\tau\vartheta) - \beta c^*(\vartheta+\mu))}{(\vartheta+\mu)(\mu+\delta)(\mu+\phi+\epsilon\varepsilon\psi c^* + \epsilon\psi i^* + \omega)}
\end{aligned}\right\} \tag{4.19}$$

When $i^* = c^* = 0$ then the expression shown in (4.19) will give disease-free equilibrium point, $E_0$.

In the absence of disease in the population (i.e. when $i^* = c^* = 0$), then the expression shown in (4.19) results to disease-free equilibrium point, $E_{0c}$ and is given by (4.20)

$$E_{0c} = (s_0, v_0, i_0, c_0, f_0, r_0) = (\frac{\omega + \mu}{\phi + \omega + \mu}, \frac{\phi}{\phi + \omega + \mu}, 0, 0, 0, 0). \tag{4.20}$$

The endemic equilibrium points that is defined as the steady state solution of the model (4.5), given by $E_c^* = (s^*, v^*, i^*, c^*, f^*, r^*)$ are shown in (4.19) when $i^* \neq 0$ and $c^* \neq 0$.

The endemic equilibrium exist when either $i^* > 0$ or $c^* > 0$ or both $i^*$ and $c^*$ are more than zero. We investigate this from (4.19).

Let $i^* > 0$ or $c^* > 0$ or both $i^* > 0$ and $c^* > 0$ then

$f^* = \frac{\xi\, i^*}{\vartheta+\mu} > 0$ since $\frac{\xi}{\vartheta+\mu} > 0$

$r^* = \frac{\tau\vartheta\xi\, i^* + \beta\, c^*(\vartheta+\mu)}{(\vartheta+\mu)(\mu+\delta)} > 0$ since all the parameters are positive.

$v^* = \frac{\phi\,((\vartheta+\mu)(\mu+\delta)(1-i^*-c^*) - i\xi\,(\delta+\mu+\tau\vartheta) - \beta\, c^*(\vartheta+\mu))}{(\vartheta+\mu)(\mu+\delta)(\mu+\phi+\epsilon\,\varepsilon\,\psi\, c^* + \epsilon\,\psi\, i^* + \omega)} > 0$

and

$s^* = \frac{(\mu+\omega+\epsilon\,\psi\, i^* + \epsilon\,\varepsilon\,\psi\, c^*)((\vartheta+\mu)(\mu+\delta)(1-i-c)) - i^*\xi\,(\delta+\mu+\tau\,\vartheta) - \beta\, c^*(\vartheta+\mu))}{(\vartheta+\mu)(\mu+\delta)(\mu+\phi+\epsilon\,\varepsilon\,\psi\, c^* + \epsilon\,\psi\, i^* + \omega)} > 0$

if

$(\vartheta+\mu)(\mu+\delta)(1-i^*-c^*) > i\xi\,(\delta+\mu+\tau\,\vartheta) + \beta\, c^*(\vartheta+\mu)$

$(1-i^*-c^*) > \frac{i\xi\,(\delta+\mu+\tau\,\vartheta) + \beta\, c^*(\vartheta+\mu)}{(\vartheta+\mu)(\mu+\delta)}$

$(1-i^*-c^*) > \frac{i\xi}{\vartheta+\mu} + \frac{i\xi\tau\,\vartheta}{(\vartheta+\mu)(\mu+\delta)} + \frac{\beta\, c^*}{\mu+\delta}$

$1 > \frac{i\xi}{\vartheta+\mu} + \frac{\beta\, c^*}{\mu+\delta}$

The last inequality is true for $i^* > 0$ and $c^* > 0$. Hence the existence of the endemic equilibrium.

### 4.3.3 Stability analysis of the disease free equilibrium

To investigate the local geometric properties of the disease free equilibria, $E_{0c}$ of (4.18), we reduce the system of (4.6) by replacing the values of $f$ and $r$ to obtain

(4.21) whose stability properties would imply to that of (4.6).

$$\left.\begin{aligned}
\tfrac{ds}{dt} &= (\mu+\alpha\, i)(1-s) + \tfrac{\delta\,(\tau\,\vartheta\,\xi\, i+\beta\, c\vartheta+\beta\, c\mu)}{(\vartheta+\mu)(\mu+\delta)} + v\omega + \alpha\, is - (\psi\, i + \epsilon\,\psi\, c + \phi)\, s \\
\tfrac{dv}{dt} &= \phi\, s + \alpha\, vi - (\omega + \epsilon\,\psi\, i + \epsilon\,\epsilon\,\psi\, c + \mu + \alpha\, i)\, v \\
\tfrac{di}{dt} &= (1-\rho)\,(\psi\, i + \epsilon\,\psi\, c)\,(s+\epsilon\, v) + \pi\, c + \tfrac{(1-\tau)\vartheta\,\xi\, i}{\vartheta+\mu} - (\alpha+\xi+\mu+\alpha\, i)\, i + \alpha\, i^2 \\
\tfrac{dc}{dt} &= \rho\,(\psi\, i + \epsilon\,\psi\, c)\,(s+\epsilon\, v) - (\pi+\beta+\mu+\alpha\, i)\, c + \alpha\, ic
\end{aligned}\right\} \tag{4.21}$$

The Model (4.21) is now studied in the region $\Psi$, where

$$\Psi = \{s, v, i, c \in R^4; 0 \le s \le 1, 0 \le v \le 1, 0 \le i \le 1, 0 \le c \le 1, 1-r-f-c-i-r \le 1\} \tag{4.22}$$

**Theorem 4.3.2** *The disease free equilibrium, $E_{0c}$ of (4.21) is locally asymptotically stable in $\Psi$ if $R_\phi < 1$ and unstable if $R_\phi > 1$.*

**Proof** Linearizing the System (4.21) around the disease free equilibrium $E_{0c}$, we obtain the matrix below.

$$J(E_0) = \begin{bmatrix}
-\mu-\phi & \omega & -\frac{(\omega+\mu)\psi}{\phi+\omega+\mu} + \frac{\delta\,\tau\,\vartheta\,\xi}{(\vartheta+\mu)(\mu+\delta)} + \alpha & -\frac{(\omega+\mu)\psi\,\epsilon}{\phi+\omega+\mu} + \frac{\delta\,\beta}{\mu+\delta} \\
\phi & -\omega-\mu & -\frac{\epsilon\,\psi\,\phi}{\phi+\omega+\mu} & -\frac{\psi\,\epsilon\,\epsilon\,\phi}{\phi+\omega+\mu} \\
0 & 0 & -\alpha-\xi-\mu+\frac{(1-\rho)P\psi}{\phi+\omega+\mu}+\frac{(1-\tau)\vartheta\,\xi}{\vartheta+\mu} & \frac{(1-\rho)P\psi\,\epsilon+\pi\,(\phi+\omega+\mu)}{\phi+\omega+\mu} \\
0 & 0 & \frac{\rho P\psi}{\phi+\omega+\mu} & -\pi-\beta-\mu+\frac{\rho\,P\psi\,\epsilon}{\phi+\omega+\mu}
\end{bmatrix}$$

where $P = \omega + \mu + \epsilon\phi$

The characteristic function of the matrix of the linearization above is defined by $det(\lambda I - J(E_{0c})) = 0$, where $I$ is the $4\times4$ identity matrix. Expanding the determinant into a characteristic polynomial we obtain the following equation equivalent to:

$$\frac{1}{(\phi+\omega+\mu)(\vartheta+\mu)}(\lambda+\mu)(\lambda+\mu+\phi+\omega)(\lambda^2+\lambda\, a_1 + a_2) = 0 \tag{4.23}$$

It is evident that the polynomial (4.23) has the negative eigenvalues:

$$\lambda_1 = -\mu,$$
$$\lambda_2 = -(\phi + \omega + \mu),$$

The third and the forth eigenvalues are given by the solutions of the quadratic equation

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

where,

$a_1 = A_5 + \frac{A_3}{A_1} - \frac{(1+\rho\epsilon-\rho)A_6\psi}{A_4}$

$a_2 = \frac{A_3A_4A_5 - \psi A_6(A_1A_2+\rho\epsilon A_3)}{A_1A_4}$

$A_1 = \vartheta + \mu$

$A_2 = \mu - \mu\rho + \pi + \beta - \rho\beta$

$A_3 = \vartheta\alpha + \vartheta\mu + \mu\alpha + \mu\xi + \mu^2 + \vartheta\xi\tau$

$A_4 = \phi + \omega + \mu$

$A_5 = \pi + \beta + \mu$

$A_6 = \mu + \epsilon\phi + \omega$

According to Hurwitz criterion, the disease free equilibrium is locally asymptotically stable if the quadratic equation has only roots with negative real parts. This is possible when both $a_1$ and $a_2$ are all positive. Expressing $a_2$ as $a_2 = \frac{A_3A_5(1-R_\phi)}{A_1}$, hence $a_2 > 0$ if $R_\phi < 1$. On the other hand, for $a_1$ to be positive,

$$\begin{aligned} A_5 + \frac{A_3}{A_1} - \frac{(1+\rho\varepsilon-\rho)R_\phi A_3A_5}{A_1A_2+\rho\epsilon A_3} &> 0 \\ A_5 + \frac{A_3}{A_1} > \frac{(1+\rho\varepsilon-\rho)R_\phi A_3A_5}{A_1A_2+\rho\varepsilon A_3} \\ A_5 + \frac{A_3}{A_1} > \frac{(1+\rho\varepsilon-\rho)R_\phi A_3A_5}{A_1A_2+A_3} \end{aligned} \tag{4.24}$$

Note: (removing $\rho\varepsilon$ which is a fraction from the denominator of RHS in the second inequality of (4.24) reduces the value of the right hand side and that in expression 2. The final expression is true and implies that $a_1 > 0$ for $R_\phi < 1$. Hence the disease-free equilibrium is locally asymptotically stable if $R_\phi < 1$ and unstable if $R_\phi > 1$

We now proceed to prove the global stability of the disease free equilibrium by means of Lyapunov function, using a quadratic linear function.

**Theorem 4.3.3** *(Castillo-Chavez & Song, 2004) The disease free equilibrium, $E_{0c}$ of (4.21) is globally asymptotically stable in $\Psi$ if $R_\phi < 1$ and unstable if $R_\phi > 1$.*

**Proof** Define the Lyapunov function $\mathcal{L}$ as;

$\mathcal{L}(s, v, i, c) = \frac{1}{2}[(s - s_0) + (v - v_0) + (i - i_0) + (c - c_0)]^2$

Then $\mathcal{L}$ is positive definite and $\mathcal{L}(s_0, v_0, i_0, c_0)$=0 and the time derivative of $\mathcal{L}$ is computed as shown below.

$\mathcal{L}' = \frac{d\mathcal{L}}{ds}\frac{ds}{dt} + \frac{d\mathcal{L}}{dv}\frac{dv}{dt} + \frac{d\mathcal{L}}{di}\frac{di}{dt} + \frac{d\mathcal{L}}{dc}\frac{dc}{dt}$

$\mathcal{L}' = [(s - s_0) + (v - v_0) + (i - i_0) + (c - c_0)][\frac{ds}{dt} + \frac{dv}{dt} + \frac{di}{dt} + \frac{dc}{dt}]$

Subtituting the derivatives of the state variable $\frac{ds}{dt}$, $\frac{dv}{dt}$, $\frac{di}{dt}$ and $\frac{dc}{dt}$ values of $i_0$ and $c_0$,we obtain;

$\mathcal{L}' = [(s - s_0) + (v - v_0) + i + c][\mu(1 - s - v) - \frac{i\mu((\mu+\delta)(\mu+\xi+\vartheta)+\tau\vartheta\xi)}{(\vartheta+\mu)(\mu+\delta)} - \frac{c\mu(\beta+\delta+\mu)}{\mu+\delta}]$

Using the fact that $\frac{\phi}{\phi+\omega+\mu} + \frac{\omega+\mu}{\phi+\omega+\mu} = s_0 + v_0 = 1$ we obtain;

$\mathcal{L}' = [(s - s_0) + (v - v_0) + i + c][\mu(s_0 + v_0 - s - v) - \frac{i\mu((\mu+\delta)(\mu+\xi+\vartheta)+\tau\vartheta\xi)}{(\vartheta+\mu)(\mu+\delta)} - \frac{c\mu(\beta+\delta+\mu)}{\mu+\delta}]$

$\mathcal{L}' = [((s - s_0) + (v - v_0)) + (i + c)][-\mu((s - s_0) + (v - v_0)) - (\frac{i\mu((\mu+\delta)(\mu+\xi+\vartheta)+\tau\vartheta\xi)}{(\vartheta+\mu)(\mu+\delta)} + \frac{c\mu(\beta+\delta+\mu)}{\mu+\delta})]$

$\mathcal{L}' < -\mu[((s - s_0) + (v - v_0)]^2 - (i + c)(\frac{i\mu((\mu+\delta)(\mu+\xi+\vartheta)+\tau\vartheta\xi)}{(\vartheta+\mu)(\mu+\delta)} + \frac{c\mu(\beta+\delta+\mu)}{\mu+\delta})$

Hence $\mathcal{L}'$ is negative definite and $\mathcal{L}' = 0$ if $s = s_0, v = v_0, i = i_0$ and $c = c_0$. Therefore the largest compact invariant set in $(s, v, i, c) \in \Gamma : \mathcal{L}' = 0$ is the singleton $E_0$. From LaSalles invariant principle (LaSalle, 1976), we conclude that $E_{0c}$ is globally asymptotically stable in the interior of $\Psi$

### 4.3.4 Asymptotic Stability of the endemic equilibrium

We investigate the asymptotic stability of the endemic equilibrium using geometric approach (Li et al., 1999). Using the spectral property of the additive compound matrices, we reproduce the following Lemma.

**Lemma 4.3.4** *Let $A$ be an $n \times n$ matrix with real entries. Then for $A$ to be stable it is necessary and sufficient that*

1. *the third additive compound matrix* $A^{[3]}$ *is stable*

2. $(-1)^n\ det(A) > 0$

The jacobian matrix for the system (4.21) at the endemic equilibrium $E_1 = (s^*, v^*, i^*, c^*)$ is:

$$J(E_1) = \begin{bmatrix} M1 & \omega & M2 & M3 \\ \phi & M4 & -\epsilon\psi v^* & -\epsilon\varepsilon\psi v^* \\ M5 & M6 & M7 & M8 \\ \rho(\psi i^* + \epsilon\psi c^*) & \rho(\psi i^* + \epsilon\psi c^*)\epsilon & \rho(s^* + \epsilon v^*)\psi & M9 \end{bmatrix}$$

where

M1$= -\mu - \psi i^* - \epsilon\psi c^* - \phi$

M2$= -s^*\psi + \alpha + \frac{\delta\tau\vartheta\xi}{(\vartheta+\mu)(\mu+\delta)}$

M3 $= -s^*\epsilon\psi + \frac{\delta\beta}{\mu+\delta}$

M4 $= -\omega - \epsilon\psi i^* - \epsilon\varepsilon\psi c^* - \mu$

M5 $= c(1-\rho) \times (\psi i^* + \varepsilon\psi c^*)$

M6$= (1-\rho)\epsilon \times (\psi i^* + \varepsilon\psi c^*)$

M7$= -\alpha - \xi - \mu + (1-\rho)(s^* + \epsilon v^*)\psi + \frac{(1-\tau)\vartheta\xi}{\vartheta+\mu}$

M8$= \pi + (1-\rho)\epsilon\psi \times (s^* + \epsilon v^*)$

M9$= -\pi - \beta - \mu + \rho\epsilon\psi \times (s^* + \epsilon v^*)$

We define the third additive compound matrix $A^{[3]}$ as

$A^{[3]} = \frac{d}{dt}|_{t=0} C_3(I + tA)$

Where

$$C_3 = \begin{bmatrix} detA[1,2,3|1,2,3] & detA[1,2,3|1,2,4] & detA[1,2,3|1,3,4] & detA[1,2,3|2,3,4] \\ detA[1,2,4|1,2,3] & detA[1,2,4|1,2,4] & detA[1,2,4|1,3,4] & detA[1,2,4|2,3,4] \\ detA[1,3,4|1,2,3] & detA[1,3,4|1,2,4] & detA[1,3,4|1,3,4] & detA[1,3,4|2,3,4] \\ detA[2,3,4|1,2,3] & detA[2,3,4|1,2,4] & detA[2,3,4|1,3,4] & detA[2,3,4|2,3,4] \end{bmatrix}$$

Giving, $A^{[3]} = \begin{bmatrix} a_{11}+a_{22}+a_{33} & a_{34} & -a_{24} & a_{14} \\ a_{43} & a_{11}+a_{22}+a_{44} & a_{23} & -a_{13} \\ -a_{42} & a_{32} & a_{11}+a_{33}+a_{44} & a_{12} \\ a_{41} & -a_{31} & a_{21} & a_{22}+a_{33}+a_{44} \end{bmatrix}$

Therefore the third additive compound for the jacobian matrix of the system (4.21) at the endemic equilibrium $J^{[3]}(E_1)$ is given by:

$$J^{[3]}(E_1) = \begin{bmatrix} J_{11} & J_{12} & J_{13} & J_{14} \\ J_{21} & J_{22} & J_{23} & J_{24} \\ J_{31} & J_{32} & J_{33} & J_{34} \\ J_{41} & J_{42} & J_{43} & J_{44} \end{bmatrix}$$

Where;

$J_{11} = -((\epsilon+1)(\varepsilon c^* + i^*) - (\epsilon v^* + s^*)(1-\rho))\psi - 3\mu - \alpha - \phi - \omega - \frac{\xi\vartheta\tau+\xi\mu}{\vartheta+\mu}$

$J_{12} = \psi\varepsilon(\epsilon v^* + s^*)(1-\rho) + \pi$

$J_{13} = \epsilon\psi v^*\epsilon$

$J_{14} = \frac{\delta\beta}{\mu+\delta} - s^*\varepsilon\psi$

$J_{21} = \psi\rho(s^* + \epsilon v^*)$

$J_{22} = -(((1+\epsilon)(\varepsilon c^* + i^*) - \rho\varepsilon(s + \epsilon v^*))\psi + 3\mu + \beta + \phi + \pi + \omega)$

$J_{23} = -\epsilon\psi v^*$

$J_{24} = s^*\psi - \alpha$

$J_{31} = -\rho(\varepsilon c^* + i^*)\epsilon\psi$

$J_{32} = \epsilon(1-\rho)\psi(\varepsilon c^* + i^*)$

$J_{33} = -\psi(i^* + \epsilon c^* - (s^* + \epsilon v^*)(1-\rho+\epsilon\rho)) - 3\mu - \pi - \alpha - \beta - \phi - \frac{\xi\vartheta\tau+\xi\mu}{\vartheta+\mu}$

$J_{34} = \omega$

$J_{41} = \psi(\epsilon c^* + i^*)\rho$

$J_{42} = -\psi(1-\rho)(\varepsilon c^* + i^*)$

$J_{43} = \phi$

$J_{44} = -\frac{\xi\vartheta\tau+\xi\mu}{\vartheta+\mu} - 3\mu - \alpha - \omega - \pi - \beta - \psi(\epsilon(\varepsilon c^* + i^*) - (s^* + \epsilon v^*)(1-\rho+\epsilon\rho))$

For $E_1 = (s^*, v^*, i^*, c^*)$ and the diagonal matrix $D = diag(s^*, v^*, i^*, c^*)$, the matrix $DJ^{[3]}(E_1)D^-$ is given by

$$-[\psi((\epsilon+1)(\varepsilon c^* + i^*) - (\epsilon v^* + s^*)(1-\rho+\varepsilon\rho)) + 3\mu + \alpha + \phi + \omega + \pi + \beta + \frac{\xi\vartheta\tau+\xi\mu}{\vartheta+\mu}]I + X$$

where $I$ is a $4 \times 4$ identity matrix and $X$ is given by

$$X = \begin{bmatrix} \frac{-\psi\rho\varepsilon(\epsilon v^*+s^*)+\pi+\beta}{1} & \frac{s^*(\psi\varepsilon(\epsilon v^*+s^*)(1-\rho)+\pi)}{v^*} & \frac{s^*\varepsilon\epsilon\psi v^*}{i^*} & \frac{s^*}{c^*}(\frac{\delta\beta}{\mu+\delta} - s^*\varepsilon\psi) \\ \frac{v^*\rho\psi(\epsilon v^*+s^*)}{s^*} & \frac{-\psi(1-\rho)(\epsilon v^*+s^*)+\alpha}{1} + \frac{\xi\vartheta\tau+\xi\mu}{\vartheta+\mu} & -\frac{v^{*2}\epsilon\psi}{i} & \frac{v^*(s\psi-\alpha)}{c^*} \\ -\frac{i\rho(\varepsilon c^*+i^*)\epsilon\psi}{s^*} & -\frac{i\epsilon(-1+\rho)\psi(\varepsilon c^*+i^*)}{v^*} & \frac{\psi\epsilon(\varepsilon c^*+i^*)+\omega}{1} & \frac{i^*\omega}{c^*} \\ \frac{c^*\psi(\varepsilon c^*+i^*)\rho}{s^*} & \frac{c\psi(-1+\rho)(\varepsilon c^*+i^*)}{v^*} & \frac{c^*\phi}{i^*} & \frac{\psi\epsilon(\varepsilon c^*+i^*)+\phi}{1} \end{bmatrix}$$

If the matrix $DJ^{[3]}D^{-1}$ is stable then $J^{[3]}$ is also stable for the similarity preserves the eigenvalues. We show that the diagonal elements of $DJ^{[3]}D^{-1}$ are all negative and the following inequalities hold.

$$\begin{aligned}
g_1 = \; & -\psi(\epsilon+1)(\varepsilon c^* + i^*) + \psi(\epsilon v^* + s^*)(1-\rho) - 3\mu - \alpha - \phi - \omega - \\
& \frac{\xi\vartheta\tau+\xi\mu}{\vartheta+\mu} + \frac{s\varepsilon\psi(\epsilon v^*+s^*)(1-\rho)}{v^*} + \frac{s^*\Pi}{v^*} + \frac{s^*\varepsilon\epsilon\psi v^*}{i^*} + s^*(\frac{\delta\beta}{\mu+\delta} - s^*\varepsilon\psi)c^{*-1} < 0 \\
g_2 = \; & \frac{v^*\rho\psi(\epsilon v^*+s^*)}{s^*} - \psi((\epsilon+1)(\varepsilon c^* + i^*) - \rho\varepsilon(\epsilon v^* + s^*)) - 3\mu - \beta - \phi - \\
& \pi - \omega - v^{*2}\epsilon\psi i^* + \frac{v^*(s^*\psi-\alpha)}{c^*} < 0 \\
g_3 = \; & -\frac{i\rho(\varepsilon c^*+i^*)\epsilon\psi}{s^*} - \frac{i^*\epsilon(-1+\rho)\psi(\varepsilon c^*+i^*)}{v^*} - \psi(\epsilon c^* + i^* - (\epsilon v^* + s^*)(1-\rho+\rho\varepsilon)) \\
& -3\mu - \pi - \alpha - \beta - \phi - \frac{\xi\vartheta\tau+\xi\mu}{\vartheta+\mu} + \frac{i^*\omega}{c^*} < 0 \\
g_4 = \; & \frac{c^*\psi(\varepsilon c^*+i)\rho}{s^*} + \frac{c^*\psi(-1+\rho)(\varepsilon c^*+i^*)}{v^*} + \frac{c^*\phi}{i^*} - \frac{\xi\vartheta\tau+\xi\mu}{\vartheta+\mu} \\
& -3\mu - \alpha - \omega - \pi - \beta - \psi(\epsilon(\varepsilon c^* + i^*) - (\epsilon v^* + s^*)(1-\rho+\rho\varepsilon)) < 0
\end{aligned} \tag{4.25}$$

Using the Loziskii measure $\mu(g)$ defined by (Li & Muldowney, 1996) as $\mu(g) = sup\{g_1, g_2, g_3, g_4\}$, and results in (4.25), we have that $\mu(g) < 0$ which implies diagonal dominance hence $J^{[3]}$ is stable according to *Gersgorin* disc (Nakatsukasa, 2011) thus verifies the first condition in Lemma 4.3.4.

To verify the second condition of the lemma, we determine the determinant of the jacobian matrix of the system at the endemic equilibrium i.e. $det(J(E_1))$.

$$det(J(E_1)) = \begin{vmatrix} -\mu - A - \phi & \omega & -s\psi + C + \alpha & -s\epsilon\psi + F \\ \phi & -\omega - A - \mu & -B + s\psi & -\epsilon\,(B - s\psi) \\ (1-\rho)\,A & (1-\rho)\,A\epsilon & -h_{1c} + (1-\rho)\,B + E & \pi + (1-\rho)\,B\epsilon \\ \rho\,A & \rho\,A\epsilon & \rho\,B & -h_{2c} + \rho\,B\epsilon \end{vmatrix}$$

where, $h_2 = \pi + \beta + \mu$

$h_1 = \alpha + \xi + \mu$

$E = \frac{(1-\tau)\vartheta\,\xi}{\vartheta+\mu}$

$F = \frac{\delta\,\beta}{\mu+\delta}$

$C = \frac{\delta\,\tau\,\vartheta\,\xi}{(\vartheta+\mu)(\mu+\delta)}$

$B = (s + \epsilon\,v)\,\psi$

$A = \psi\,i + \epsilon\,\psi\,c$

$$det(J(E_{1c})) = \left\{ \begin{array}{c} \frac{X\left((\mu+A)\rho\,\epsilon\,s\psi\,A(1-\epsilon)+A^2(h_{2c}-\rho\,F)+(Ah_{2c}+\mu\,h_{2c}-B\mu\,\rho\,\epsilon)(\omega+\phi+\mu)\right)}{\vartheta+\mu} + \\ (\beta+\mu)\left((1-\epsilon)\,(AB\rho\,(\mu+\phi) + A^2B\rho - A\psi\,s\rho\,(\mu+A)) + B\mu^2\rho\right) \\ +A^2\rho\,(\alpha+C)\,(\beta+\mu) + A^2\psi\,s\,(1-\epsilon)\,h_2 + s\psi\,\mu\,(1-\epsilon)\,Ah_2 \end{array} \right\}$$

$$- \left\{ \begin{array}{c} \frac{((\alpha\,(\vartheta+\mu)(\mu+\delta)+\delta\,\tau\,\vartheta\,\xi)((1-\rho)(\beta+\mu)+\pi+Ah_{2c})+X\delta\,\beta\,\rho)A(\phi\,\epsilon+\omega+\mu)}{\vartheta(\mu+\delta)+\mu(\mu+\delta)} \\ +B\mu\,(\omega+\phi)\,((1-\rho)\,(\beta+\mu)+\pi) \\ +AB\,(1-\epsilon)\left(\frac{\rho(A+\mu+\phi)\epsilon(A+\mu+\phi)X(A+\mu+\phi)}{\vartheta(A+\mu+\phi)+\mu(A+\mu+\phi)} + h_{2c}\,(A+\mu+\phi)\right) + B\mu^2h_{2c} \end{array} \right\}$$

where

$X = \alpha\,\vartheta + \alpha\,\mu + \xi\,\mu + \vartheta\,\mu + \mu^2 + \xi\,\vartheta\,\tau$

and since,

$$\left\{\begin{array}{c} \frac{X\left((\mu+A)\rho\,\epsilon\,s\psi\,A(1-\epsilon)+A^2(h_{2c}-\rho\,F)+(Ah_2+\mu\,h_2-B\mu\,\rho\,\epsilon)(\omega+\phi+\mu)\right)}{\vartheta+\mu}+ \\ (\beta+\mu)\left((1-\epsilon)\left(AB\rho\,(\mu+\phi)+A^2B\rho-A\psi\,s\rho\,(\mu+A)\right)+B\mu^2\rho\right) \\ +A^2\rho\,(\alpha+C)\,(\beta+\mu)+A^2\psi\,s\,(1-\epsilon)\,h_{2c}+s\psi\,\mu\,(1-\epsilon)\,Ah_{2c} \end{array}\right\}$$

$$> \left\{\begin{array}{c} \frac{((\alpha\,(\vartheta+\mu)(\mu+\delta)+\delta\,\tau\,\vartheta\,\xi)((1-\rho)(\beta+\mu)+\Pi+Ah_{2c})+X\delta\,\beta\,\rho)A(\phi\,\epsilon+\omega+\mu)}{\vartheta(\mu+\delta)+\mu(\mu+\delta)} \\ +B\mu\,(\omega+\phi)\left((1-\rho)\,(\beta+\mu)+\pi\right) \\ +AB\,(1-\epsilon)\left(\frac{\rho(A+\mu+\phi)\epsilon(A+\mu+\phi)X(A+\mu+\phi)}{\vartheta(A+\mu+\phi)+\mu(A+\mu+\phi)}+h_{2c}\,(A+\mu+\phi)\right)+B\mu^2h_{2c} \end{array}\right\}$$

$det(J(E_{1c})) > 0$ which satisfies the second condition. We therefore conclude that the endemic equilibrium is asymptotically stable.

### 4.3.5 Analysis of the system in a carrier free population at endemic equilibrium

Considering a carrier-free population (when $\beta \to \infty$) then from (4.8) we can define the new basic reproduction number $R_{c_0}(\phi)$ as

$$R_{c_0}(\phi) = \lim_{\beta\to\infty} R_\phi \tag{4.26}$$

$$R_{c_0}(\phi) = \left[\frac{\mu+\epsilon\,\phi+\omega}{\phi+\omega+\mu}\right]\left[\frac{\psi\,(1-\rho)(\mu+\vartheta)}{\vartheta\,\alpha+\vartheta\,\mu+\mu\,\alpha+\mu\,\xi+\mu^2+\vartheta\,\xi\,\tau}\right] \tag{4.27}$$

On comparing $R_{c_0}(\phi)$ and $R_\phi$, it is simple to show that $R_{c_0}(\phi) < R_\phi$ since

$$-\mu\,\rho\,\pi-\vartheta\,\rho\,\pi < \rho\,\epsilon\,(\vartheta\,\alpha+\vartheta\,\mu+\mu\,\alpha+\mu\,\xi+\mu^2+\vartheta\,\xi\,\tau)$$

The solution of the proportion of symptomatically infected individuals $i$ at endemic equilibrium in a carrier-free population is determined by the cubic equation in (4.28).

$$\left.\begin{aligned}
&-\left[\frac{\psi\epsilon(\vartheta\mu+\mu\xi+\mu^2+\vartheta\xi\tau+\xi\delta+\mu\delta+\vartheta\delta)}{(\mu+\epsilon\phi+\omega)(\mu+\vartheta)}R_{C0}\right]i^3\\
&-\left[\frac{\psi\epsilon(\mu+\delta)}{\mu+\epsilon\phi+\omega}\left(\frac{\mu+\epsilon\phi+\omega}{\mu+\phi+\omega}-R_{C0}\right)+\left(\frac{1+\xi\delta}{\mu+\vartheta}+\alpha+\delta\right)R_{c0}\right]i^2\\
&-[(\mu+\delta)(1-R_{c0})]i=0
\end{aligned}\right\} \tag{4.28}$$

Equation (4.28) can be written as

$$ai^3+bi^2+ci=0 \tag{4.29}$$

where

$$\left.\begin{aligned}
a&=-\left[\frac{\psi\epsilon(\vartheta\mu+\mu\xi+\mu^2+\vartheta\xi\tau+\xi\delta+\mu\delta+\vartheta\delta)}{(\mu+\epsilon\phi+\omega)(\mu+\vartheta)}R_{C0}\right]\\
b&=-\left[\frac{\psi\epsilon(\mu+\delta)}{\mu+\epsilon\phi+\omega}\left(\frac{\mu+\epsilon\phi+\omega}{\mu+\phi+\omega}-R_{C0}\right)+\left(\frac{1+\xi\delta}{\mu+\vartheta}+\alpha+\delta\right)R_{C0}\right]\\
c&=-[(\mu+\delta)(1-R_{C0})]
\end{aligned}\right\} \tag{4.30}$$

One of the solutions for (4.28) for $i$ is zero implying a disease-free equilibrium solution, while the other two solutions are determined by the quadratic Equation (4.31)

$$ai^2+bi+c=0 \tag{4.31}$$

The solution of (4.31) is $i=\frac{-b\pm\sqrt{b^2-4ac}}{2a}$. For $R_{C0}>1$ we determine the signs of the quadratic coefficients in (4.31) as $a<0$, $b<0$ and $c>0$.

Since $a<0$, the parabola of (4.31) will open downwards. Now let $D=b^2-4ac$, then by using results in (4.30) $D>0$ indicating that there are two solutions for $i$ ($i_1$ and $i_2$). There are three possible interpretations of $i_1$ and $i_2$ depending on their signs.

Case1: if $i_1>0$ and $i_2>0$ then there are two endemic equilibrium.

Case 2: if either $i_1$ or $i_2$ is less than zero then there is only one endemic equilibrium.

Case 3: if $i_1<0$ and $i_2<0$ then there is no endemic equilibrium point, hence only

the disease-free equilibrium will exist. We therefore conclude that in a carrier-free population, there is one endemic equilibrium point and a disease-free when $R_{C0} > 1$, and only a disease-free when $R_{C0} < 1$

## 4.4 Numerical Simulation

We conduct a numerical simulation to show the sensitivity of $R_0$ based on the variation of the model parameters. We also show the existence of equilibrium values as well as the feasibility of stability conditions for a set of parameters. Simulation is done by MAPLE 16.0 using the parameters shown in table 4.2. Win Bugs simulation software is also used to simulate the variation of $R_0$ using Markov Chain Monte Carlo(MCMC) approach.

### 4.4.1 A probability estimation of the Basic Reproduction number in the presence of control measures

The basic reproduction number is defined as the expected number of secondary infections realized when an infected individual is introduced into a purely susceptible population. It is one of the most important concern parameter for a disease to invade a population (Heffernan et al., 2005). From the definition, it is definitely clear that when $R_0 < 1$, each infected individual produces less than one newly infected individual on an average and therefore there is a possibility that the infection will be cleared from the population. We therefore determine which control measures and at what magnitude would reduce $R_0$ below one at a greater percentage. This will provide vital information to the public health initiatives.

The conventional method of determining the basic reproduction number is based on deterministic models where the basic reproduction number is expressed as a single

value computed from the expression of parameter which are also estimated as single value. Considering now that the transmission parameters are random variables assuming some probability distribution, then it would be possible tpo compute the probability distribution of the basic reproduction number.

Consider now the basic reproduction numbers $R_o$(*No control measures used*) $R_\phi$ (*when vaccination alone is used* ), $R_\tau$(*when treatment alone is used* ) and , $R_{\tau\phi}$(when treatment alone is used ). These reproduction numbers are derived from a mathematical model (4.1). They are a function of many parameters. When we compute the values of the basic reproduction numbers using single values of the parameters, then the result is a single value. Since each of the model's parameters are assumed to be uncertain, we consider the parameters to take the form of a random variable and follow particular probability distributions. We therefore use Monte Carlo simulation techniques to study the probability distribution of the basic reproduction number with the random effects when the parameters with assumed probability distribution are used .

A probability density function is assigned to each parameter based on their possible values and probability of occurrence of any specific value. The possible values of the parameters are estimated from literature (see Table 4.2). The parameters with peak values are considered to follow approximately triangular probability distribution while those without peak values assumed to follow approximately uniform probability distribution. Monte Carlo Markov Chain simulation methods employ the most appropriate sampling scheme resulting into $N = 10,000$ samples for each parameter. The histograms for the parameters are constructed as shown in Figure 4.2.

The empirical probability values calculated when the basic reproduction numbers is less than one and when more than one after 10,000 runs for the Monte Carlo Simulation is shown in the Table 4.3.

The histograms corresponding to the results in Table 4.3 for $R_\phi$, $R_\tau$, $R_{\tau\phi}$ and $R_o$ are obtained as shown in Figure 4.3 and their fitted probability distributions for the basic reproduction number is superimposed on the histograms.

The probability density functions for $R_o$, $R_\tau$, $R_\phi$ and $R_\phi\tau$ that best fit the simulated data are estimated using Kernel density estimation approach whose optimal kernel functions are chosen to be Epanechnikov while the corresponding bandwidth shown in Table 4.4 are based on how best the density fits the data.

On comparison of the density function of the basic reproduction numbers, $R_o$, $R_\tau$, $R_\phi$ and $R_\phi\tau$, it is noted in Figure 4.4.

The results in Figure 4.4 indicate that the chances that the basic reproduction will be less than 1 when both vaccination and treatment strategies are used, is higher than when one of the strategies ( vaccination and treatment) is used respectively which are also higher when non of the strategies (vaccination and treatment) are used.

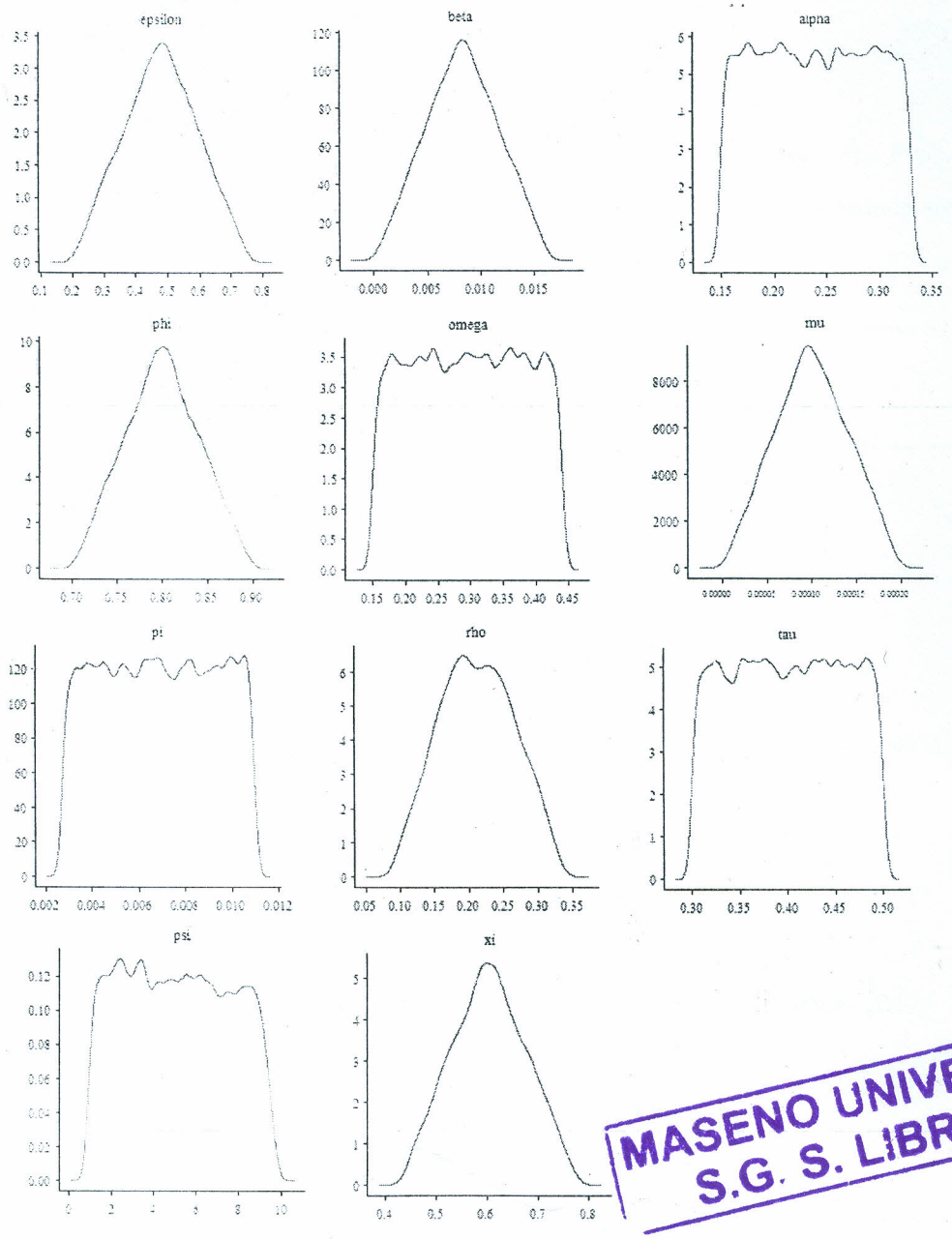




Figure 4.2: Kernel density functions of the values obtained from MCMC sampling procedure for the input parameters (the remaining parameters whose histograms are not shown here are assumed to have constant values)

Table 4.2: The model parameter values and distributions of percentages: The Probability Distribution are either uniform(when the minimum and maximum values are given) ot triangular (when peak values are given

)

| Par | Unit | Values | | | Reference |
|---|---|---|---|---|---|
| | | Min | Peak | Max | |
| $\nu$ | | | $\mu N_0$ | | (Doura et al., 2000) |
| $\kappa$ | /day | 1 | | 10 | Estimated |
| $\mathcal{P}$ | | 0.89 | | 0.99 | (Doura et al., 2000) |
| $\psi$ | | | $\kappa\mathcal{P}$ | | Expressed as in (3.2) |
| $\varepsilon$ | | | 0.001124 | | (Doura et al., 2000) |
| $\rho$ | | 0.085 | 0.28 | 0.338 | (Bakir et al., 2002; Gazi et al., 2004) |
| $\pi$ | /day | 0.00274 | | 0.01096 | (Doura et al., 2000) |
| $\eta$ | /day | 0.0238 | | 0.0476 | (Thadani, 2011) |
| $\alpha$ | | 0.15 | | 0.33 | Estimated |
| $\delta$ | | 0 | | 0.3 | Estimated |
| $\mu$ | /day | 0 | 0.00004793 | 0.0002 | (World Health Organization, 2010) |
| $\beta$ | | 0 | 0.0115 | 0.0165 | (Hill et al., 2008) |
| $\phi$ | | 0.7 | 0.8 | 0.9 | (GAVI, 2011) |
| $\omega$ | | 0.15 | | 0.44 | (Kuhlmann et al., 2012) |
| $\epsilon$ | | 0.2 | 0.48 | 0.76 | (Aslan et al., 2007) |
| $\tau$ | | 0.3 | | 0.5 | Estimated |
| $\xi$ | | 0.43 | 0.56 | 0.78 | (Gazi et al., 2004) |

Table 4.3: The empirical probability values when the basic reproduction number is less that one and when more than one

| | Counts | Empirical probability | |
|---|---|---|---|
| | less than 1 | percent less than 1 | percent more than 1 |
| $R_o$ | 52 | 0.52 | 99.48 |
| $R_\tau$ | 2889 | 28.89 | 71.11 |
| $R_\phi$ | 3755 | 37.55 | 62.45 |
| $R_{\phi\tau}$ | 4836 | 48.36 | 51.64 |

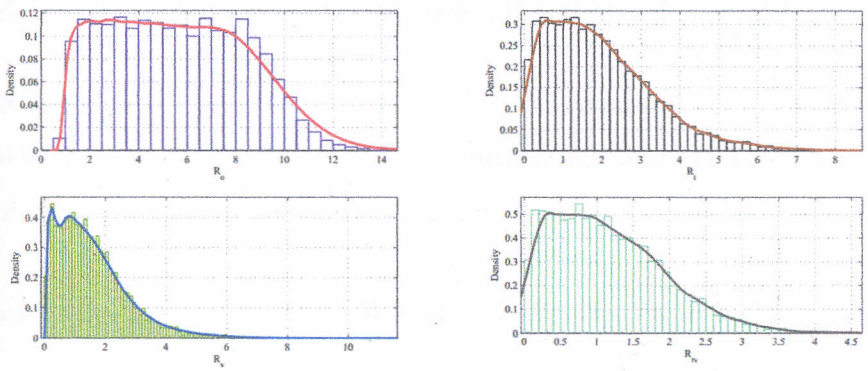


Figure 4.3: Histograms and probability density functions of $R_o$, $R_\tau$, $R_\phi$ and $R_{\phi\tau}$ of pneumonia model

Table 4.4: Bandwidth of the estimated density functions

| Basic reproduction number | Bandwidth |
|---|---|
| $R_o$ | 0.120 |
| $R_\tau$ | 0.135 |
| $R_\phi$ | 0.223 |
| $R_{\phi\tau}$ | 0.136 |

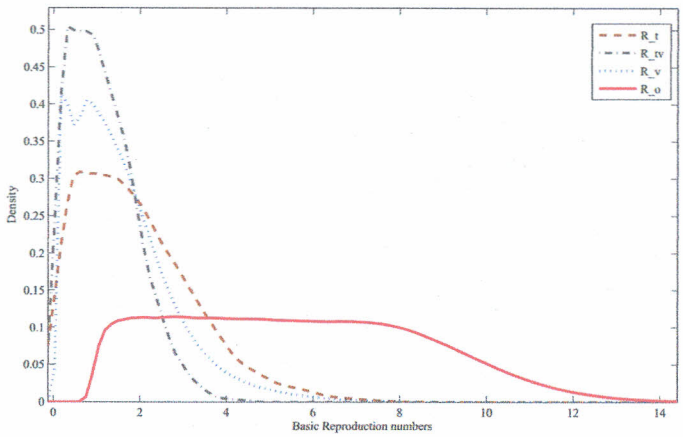


Figure 4.4: Probability density functions of $R_o$, $R_\tau$, $R_\phi$ and $R_\phi\tau$ of pneumonia model

### 4.4.2 Fitting probability distribution of $R_o$, $R_\tau$, $R_\phi$ and $R_\phi\tau$

Fitting probability distribution to a data set is a common task in statistics and consist if selecting candidates probability distribution, modeling the random variable as well as finding the parameters for that distribution.

#### Candidate probability distribution for $R_o$, $R_\tau$, $R_\phi$ and $R_\phi\tau$

The candidate for each of the basic reproduction numbers is determined using the skewness-kurtosis plot (Cullen & Frey, 2002). The Figures (4.5, 4.6, 4.7 and 4.8) show the skewness-kurtosis plots indicating possible probability distribution candidates for $R_o$, $R_\tau$, $R_\phi$ and $R_\phi\tau$ respectively.

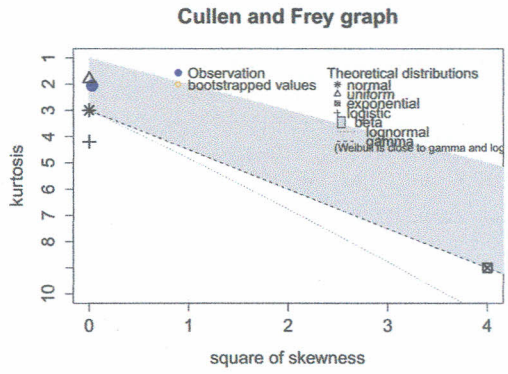


Figure 4.5: Candidates Probability density functions of $R_o$. Candidates are: Uniform, Normal and Logistic

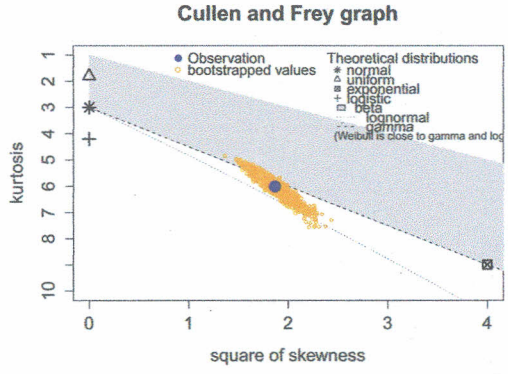


Figure 4.6: Candidates Probability density functions of $R_\tau$. Candidates are: Gamma, LogNormal and Weibull

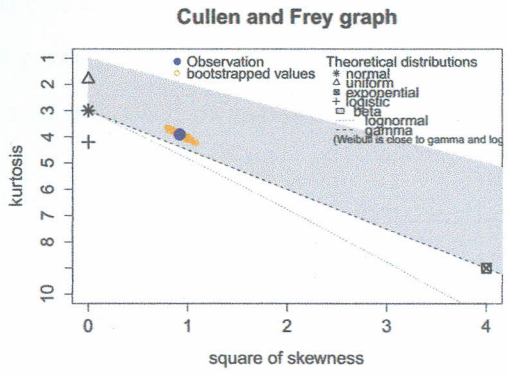


Figure 4.7: Candidates Probability density functions of $R_{\phi}$. Candidates are: Gamma, LogNormal and Weibull

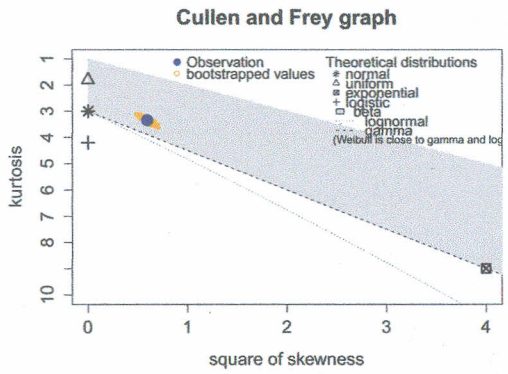


Figure 4.8: Candidates Probability density functions of $R_{\tau\phi}$. Candidates are: Gamma, LogNormal and Weibull

Based on the selected candidate parametric distributions $f(. \mid \Theta)$, the data are then fitted using the MLE method. Under the $i.i.d$ sample assumptions, distribution parameter $\Theta$ are by default estimated by maximizing the likelihood function defined by

$$L(\Theta) = \prod_{i=1}^{n} (x_o \mid \Theta) \tag{4.32}$$

The candidate are then fitted to the data set as shown in Figures (4.9, 4.10, 4.11 and 4.12) and then goodness of fit is used to select the best fit candidates.

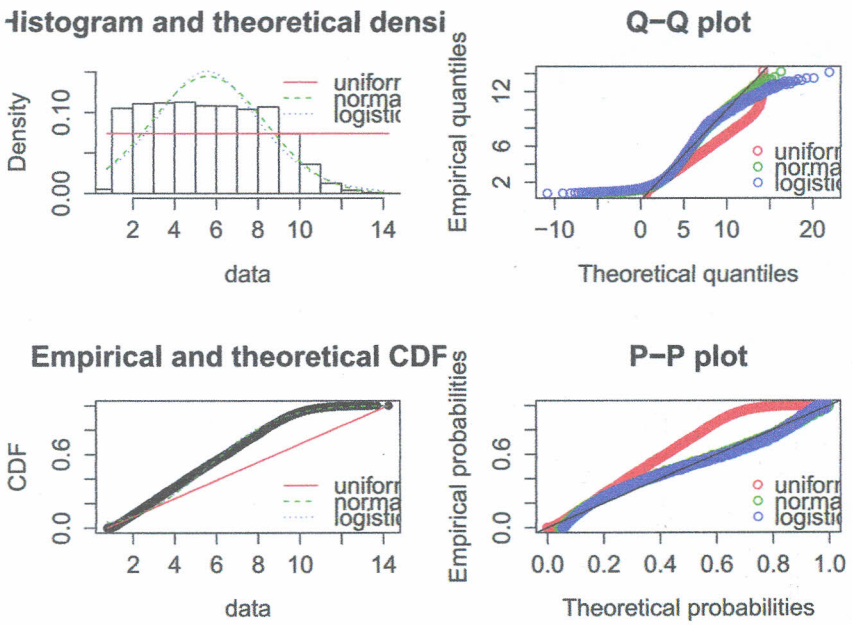


Figure 4.9: Goodness of fit for the candidates dist for $R_o$. Best fits are: Normal and Logistic

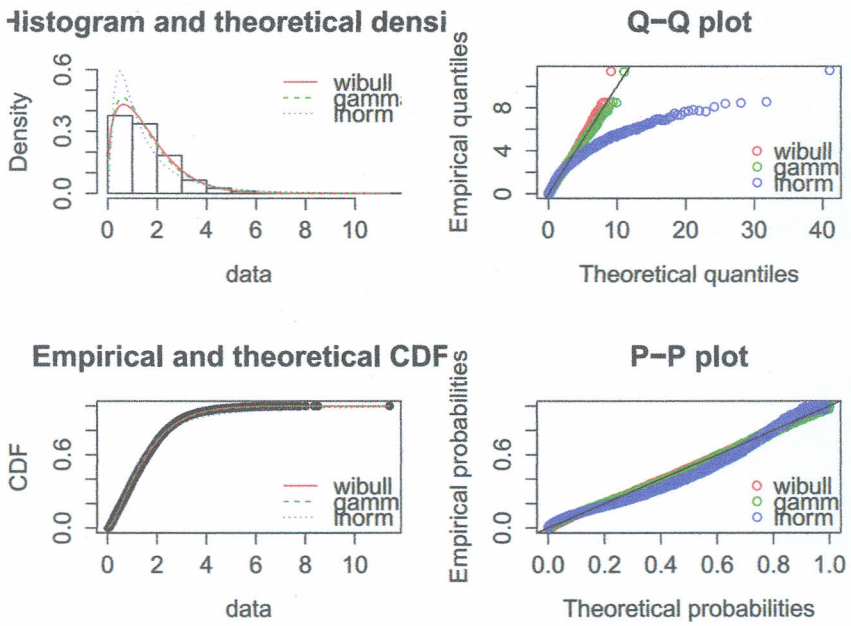


Figure 4.10: Goodness of fit for the candidates dist for $R_\tau$. Best fits are: Weibull and Gamma

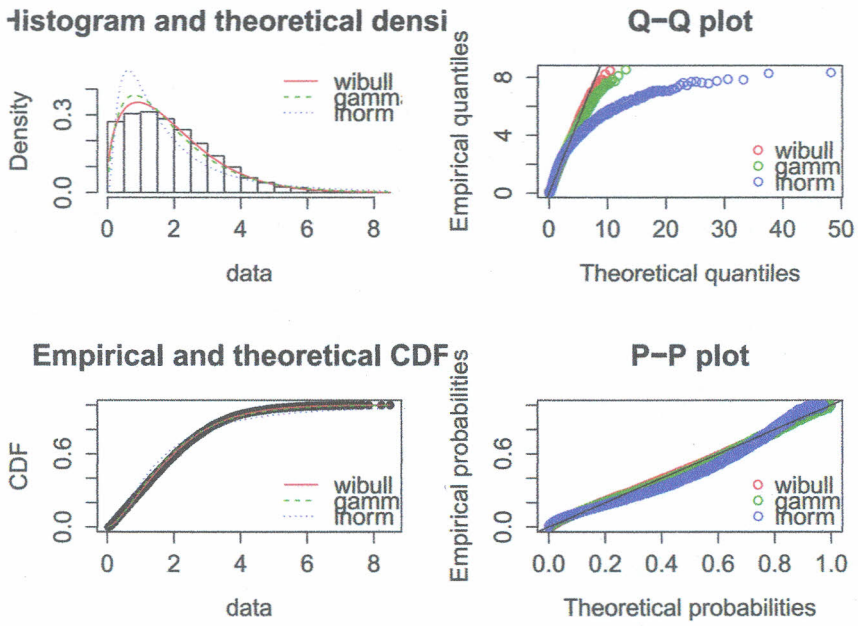


Figure 4.11: Goodness of fit for the candidates dist for $R_\phi$. Best fits are: Weibull and Gamma

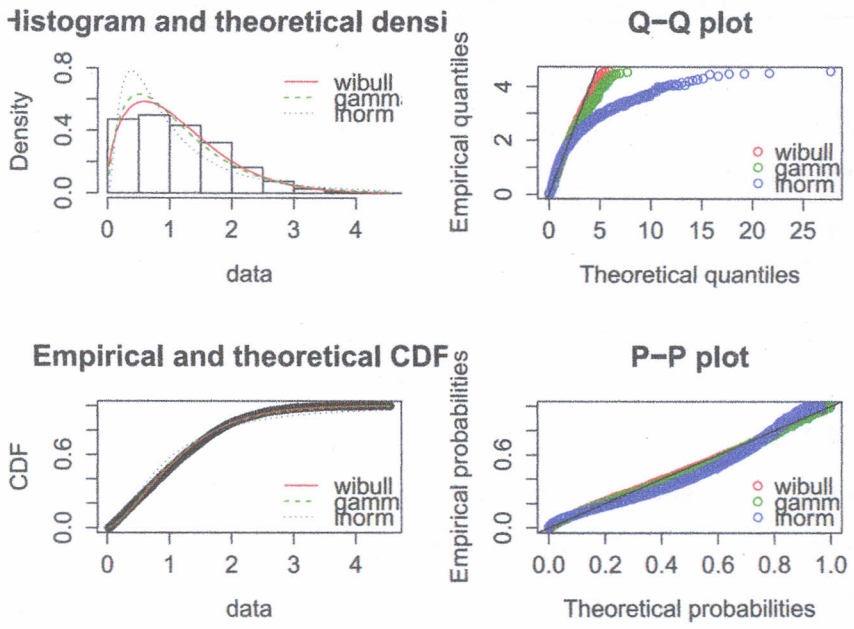


Figure 4.12: Goodness of fit for the candidates dist for $R_\phi\tau$. Best fits are: Weibull and Gamma

Results in Figures (4.9, 4.10, 4.11 and 4.12) identifies two parametric distribution for each basic reproduction numbers. On further analysis using the goodness of fit statistics, Aic and Bic are applied to choose the best distribution out of the two candidates as shown Tables (4.4.2 & 4.4.2 ).

Table 4.5: Goodness of fit statistics for $R_o$ and $R_\tau$.

| criteria | $R_o$ | | $R_\tau$ | | |
|---|---|---|---|---|---|
| | norm | logis | weibull | gamma | lnorm |
| Aic | 48646.12 | 49405.54 | 27497.79 | 27566.05 | 29030.73 |
| Bic | 8660.54 | 49419.96 | 27512.21 | 27580.47 | 29045.15 |

Candidates with the lowest Aic and Bic are selected as the best fit probability distributions. Hence the basic reproduction number are distributed according the probability distributions listed in Table 4.4.2.

Table 4.6: Goodness of fit statistics for $R_\phi$ and $R_{\tau\phi}$.

| criteria | $R_\phi$ | | | $R_{\tau\phi}$ | | |
|---|---|---|---|---|---|---|
| | weibull | gamma | lnorm | weibull | gamma | lnorm |
| Aic | 31327.27 | 31524.40 | 33215.26 | 20763.81 | 21061.98 | 22904.27 |
| Bic | 31341.69 | 31538.82 | 33229.69 | 20778.23 | 21076.40 | 22918.69 |

Table 4.7: Probability distributions for $R_o$, $R_\tau$, $R_\phi$ and $R_{\tau\phi}$.

| R | Distribution | Parameter1 | Parameter 2 |
|---|---|---|---|
| $R_o$ | Normal | mean=5.605 ($\pm$ 0.0275) | sd =2.755 ($\pm$ 0.0195) |
| $R_\tau$ | Weibull | Shape= 1.430 ($\pm$0.0113) | Scale=2.111 ($\pm$0.0155) |
| $R_\phi$ | Weibull | Shape=1.363 ($\pm$0.0106) | Scale=1.701 ($\pm$0.0131) |
| $R_{\tau\phi}$ | Weibull | Shape=1.483 ($\pm$0.0119) | Scale=1.269 ($\pm$0.0090) |

The value of the basic reproduction number, R is a useful indicator because it helps to determine whether or not an infectious disease can spread through a population. When $R < 1$ then the infection will die out in the long run. But if $R > 1$ then the infection will be able to spread in a population. Using the results in Table 4.8, we show that the probability that the infection spread in the population by computing $Pr(R > 1)$. Results in Table 4.8 indicate that chances of pneumonia epidemics is lowest when both vaccination and treatment strategies are used.

Table 4.8: Mean, sd, chance of disease epidemic using the Selected probability distribution

| R | Mean | SD | $pr(R > 1)$ |
|---|---|---|---|
| $R_o$ | 5.605 | 2.755 | 0.9527083 |
| $R_\tau$ | 1.917841 | 1.360551 | 0.7093538 |
| $R_\phi$ | 1.556886 | 1.155063 | 0.615811 |
| $R_{\phi\tau}$ | 1.146789 | 0.7866684 | 0.4952729 |

A correlation coefficient is calculated between the values of each of the parameters in Table 4.9 and the values of the basic reproduction number ($R_\phi$ and $R_\tau$) to check the sensitivity (statistical influence) of each of the parameter on the basic reproduction number. Since we lack historical data of the parameters, we make the assumptions of statistical independence of the input parameter.

Results in Table 4.9 indicate that when all the control strategies are considered, basic reproduction number($R_\phi$) is significantly an increasing function with the effective contact rate $\psi$, proportion of uncovered strain in the vaccine $\epsilon$, rate at which the vaccine wanes $\omega$ and the rate at which Carriers become symptomatically infectious $\pi$. It is also noted that both $R_\phi$ and $R_\tau$ are decreasing functions with treatment efficacy $\tau$ and rate of joining the treated class $\xi$

Table 4.9: Correlation coefficient for the basic reproduction number ($R_\phi$ & $R_\tau$) and each input parameter variable.

| | R($\tau$) | | R($\phi$) | |
|---|---|---|---|---|
| | Corr | P-Value | Corr | P-Value |
| $\alpha$ | -0.2134 | 0.0000 | -0.2074 | 0.0000 |
| $\beta$ | -0.052 | 0.0000 | -0.0413 | 0.0000 |
| $\epsilon$ | | | 0.2548 | 0.0000 |
| $\mu$ | -0.0195 | 0.0515 | -0.0127 | 0.2026 |
| $\omega$ | | | 0.0948 | 0.0000 |
| $\phi$ | | | -0.0095 | 0.3443 |
| $\pi$ | 0.0392 | 0.0001 | 0.0354 | 0.0004 |
| $\psi$ | 0.9415 | 0.0000 | 0.8975 | 0.0000 |
| $\rho$ | -0.0702 | 0.0000 | -0.0703 | 0.0000 |
| $\tau$ | -0.1464 | 0.0000 | -0.1381 | 0.0000 |
| $\xi$ | -0.125 | 0.0000 | -0.1178 | 0.0000 |

### 4.4.3 Optimal Control Strategy

Using MCMC simulation, we obtain the optimal vaccination strategy and treatment strategy for pneumonia. Using the parameter variables associated with the the vaccination and treatments respectively at different values, we determine at what value of the parameters will the basic reproduction be at lowest. The parameters are classified into two namely:vaccination parameter($\phi$, $\omega$ and $\epsilon$) and treatment parameters ($\xi$ and $\tau$).

#### Optimal vaccination Strategy

Consider different strategies for computing $R_\phi$ at different parameter value segments of $\phi$, $\omega$ and $\epsilon$ as described in Table A.1. The segments of the parameter values are assumed to be uniformly distribution within the range of the values given which are defined as in Table 4.10

Table 4.10: Vaccination parameter segments for computing $R_\phi$

| Segment | $\epsilon$ | $\omega$ | $\phi$ |
|---|---|---|---|
| 1 | $\epsilon \sim$ U(0.0,0.20) | $\omega \sim$ U(0.00,0.15) | $\phi \sim$ U(0.4,0.6) |
| 2 | $\epsilon \sim$ U(0.20,0.39) | $\omega \sim$ U(0.15,0.25) | $\phi \sim$ U(0.6,0.7) |
| 3 | $\epsilon \sim$ U(0.39,0.57) | $\omega \sim$ U(0.25,0.35) | $\phi \sim$ U(0.7,0.8) |
| 4 | $\epsilon \sim$ U(0.57,0.78) | $\omega \sim$ U(0.35,0.45) | $\phi \sim$ U(0.8,1.0) |

WinBugs is used to compute the aggregate value of R($\phi$) for different strategies described in Table A.1.

The results of the analysis of variance (ANOVA) to test whether the vaccination parameters have significant effect on R($\phi$) is shown in Table 4.11. The liear model for consideration is:

$Y_{ijkn} = \mu + \phi_i + \omega_j + \epsilon_k + (\epsilon\omega)_{ij} + (\epsilon\phi)_{ik} + (\omega\phi)_{jk} + (\epsilon\omega\phi)_{ijk} + \varepsilon_{ijkn}$

Where;

$Y_{ijkn} = R_\phi$ Basic reproductive number

$\phi_i$ , $\omega_j$ ,$\epsilon_k$ are main effect of the parameters (in whole plot, sub plot and sub-sub plot respectively)

$(\epsilon\omega)_{ij}$, $(\epsilon\phi)_{ik}$, $(\omega\phi)_{jk}$ are two way interaction effects

$(\epsilon\omega\phi)_{ijk}$ in the three way interaction effect

$\varepsilon_{ijkn} \sim N(0, \sigma^2)$ independent random variables.

Table 4.11: Analysis of variance for the effect of Vaccination parameter on $R_\phi$

| Variate: $R_o$ | | | | | |
|---|---|---|---|---|---|
| Source of var | d.f. | s.s. | m.s. | v.r. | F pr. |
| Rep stratum | 999 | 1.080E+04 | 1.081E+01 | 922.38 | |
| $\phi$ | 3 | 1.267E+02 | 4.223E+01 | 3602.15 | <0.001 |
| Residual | 2997 | 3.514E+01 | 1.172E-02 | 0.60 | |
| $\omega$ | 3 | 8.907E+02 | 2.969E+02 | 15089.22 | <0.001 |
| $\phi.\omega$ | 9 | 1.290E+01 | 1.433E+00 | 72.84 | <0.001 |
| Residual | 11988 | 2.359E+02 | 1.968E-02 | 0.71 | |
| $\epsilon$ | 3 | 5.820E+03 | 1.940E+03 | 70345.60 | <0.001 |
| $\phi.\epsilon$ | 9 | 1.548E+01 | 1.720E+00 | 62.36 | <0.001 |
| $\omega.\epsilon$ | 9 | 1.089E+02 | 1.209E+01 | 438.57 | <0.001 |
| $\phi.\omega.\epsilon$ | 27 | 1.589E+00 | 5.886E-02 | 2.13 | <0.001 |
| Residual | 47952 | 1.322E+03 | 2.758E-02 | | |
| Total | 63999 | 1.937E+04 | | | |

All the three vaccination parameters are having significant effect on R($\phi$) since their P-values are less than 0.001 (P-value $< 0.001$). All the interactions of two parameters are also significant, however the interaction of three parameters at once is not significant. This indicates that the value of R($\phi$) is guaranteed to change significantly when, the either of the vaccination parameters are changed individually or pair of the parameters are changed.

From 1000 samples generated we computed the proportion of the samples having their R($\phi$)$\leq$ 1 (see Table 4.12). The results shows that using vaccination strategy 4 has the lowest chance that the disease will invade the population followed by strategy 3 and so on.

Table 4.12: The empirical probabilities $R_\phi \leq 1$ according to the strategies described in Table A.1

| | phi | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| epsilon | omega | | | | |
| 1 | 1 | 49% | 56% | 61% | 67% |
| 1 | 2 | 11% | 17% | 21% | 26% |
| 1 | 3 | 6% | 9% | 12% | 16% |
| 1 | 4 | 3% | 6% | 7% | 10% |
| 2 | 1 | 6% | 7% | 8% | 8% |
| 2 | 2 | 2% | 3% | 4% | 4% |
| 2 | 3 | 1% | 2% | 2% | 3% |
| 2 | 4 | 1% | 1% | 1% | 2% |
| 3 | 1 | 8% | 9% | 9% | 10% |
| 3 | 2 | 2% | 4% | 4% | 5% |
| 3 | 3 | 2% | 2% | 2% | 3% |
| 3 | 4 | 1% | 1% | 2% | 2% |
| 4 | 1 | 0% | 0% | 0% | 0% |
| 4 | 2 | 0% | 0% | 0% | 0% |
| 4 | 3 | 0% | 0% | 0% | 0% |
| 4 | 4 | 0% | 0% | 0% | 0% |

### Optimal treatment Strategy

Now by considering treatment strategy, the parameters ($\xi$ and $\tau$) are used at different range of values to compute $R_\phi$. Each of the parameters are divided into four segments and assumed to be uniformly distributed over the range as described in Table 4.13.

Table 4.13: Treatment parameter segments for computing $R_\phi$

| Segment | $\xi$ | $\tau$ |
|---|---|---|
| 1 | $\xi \sim$ U(0.0,0.25) | $\tau \sim$ U(0.0,0.25) |
| 2 | $\xi \sim$ U(0.25,0.50) | $\tau \sim$ U(0.25,0.50) |
| 3 | $\xi \sim$ U(0.50,0.75) | $\tau \sim$ U(0.50,0.75) |
| 4 | $\xi \sim$ U(0.75,1.0) | $\tau \sim$ U(0.75,1.0) |

There would be 16 different combinations for computing the $R_\phi$ as shown in Table A.2 hence we consider the effect of 16 strategies of treatment on $R_\phi$. On the analysis of variance in Table 4.14 , there is no significant evidence that the rate of treatment uptake, $\xi$ and treatment efficacy, $\tau$ will have effect on $R_\phi$.

Table 4.14: Analysis of variance for the effect of Treatment parameter on $R_\phi$

**Analysis of variance**
Variate: $R_\phi$

| Source of variation | d.f. | s.s. | m.s. | v.r. | F pr. |
|---|---|---|---|---|---|
| rep stratum | | | | | |
| $\tau$ | 3 | 410.66 | 136.89 | 0.57 | 0.635 |
| $\xi$ | 3 | 173.07 | 57.69 | 0.24 | 0.868 |
| $\tau.\xi$ | 9 | 652.65 | 72.52 | 0.3 | 0.974 |
| Residual | 984 | 236489.72 | 240.34 | 20.46 | |
| rep.*Units* stratum | | | | | |
| $\xi$ | 3 | 21,82 | 7.27 | 0.62 | 0.602 |
| $\tau.\xi$ | 9 | 31.83 | 3.54 | 0.3 | 0.975 |
| Residual | 14988 | 176048.64 | 11.75 | | |
| Total | 15999 | 413828.39 | | | |

The results in Table 4.14 indicates that, given the treatment efficacy or/and rate of treatment is improved, there is no guarantee that the value of $R_\phi$ will be reduced.

### 4.4.4 Effects of the vaccination parameters on susceptible and infected classes.

During the colonization stage, pneumococcus may successfully establish an infection or be cleared by ones immune response. It is therefore important to note that this stage always precedes infection. Most individuals are able to clear these transient colonies, although some cannot without the aid of vaccination. Considering the vaccination parameters used in the model: vaccination uptake $\phi$, the probability that the vaccine wanes $\omega$ and the proportion serotype that are not covered in the vaccine $\epsilon$, we estimate their optimal level when the infection rate is lowest. The results are shown in Figure 4.13.

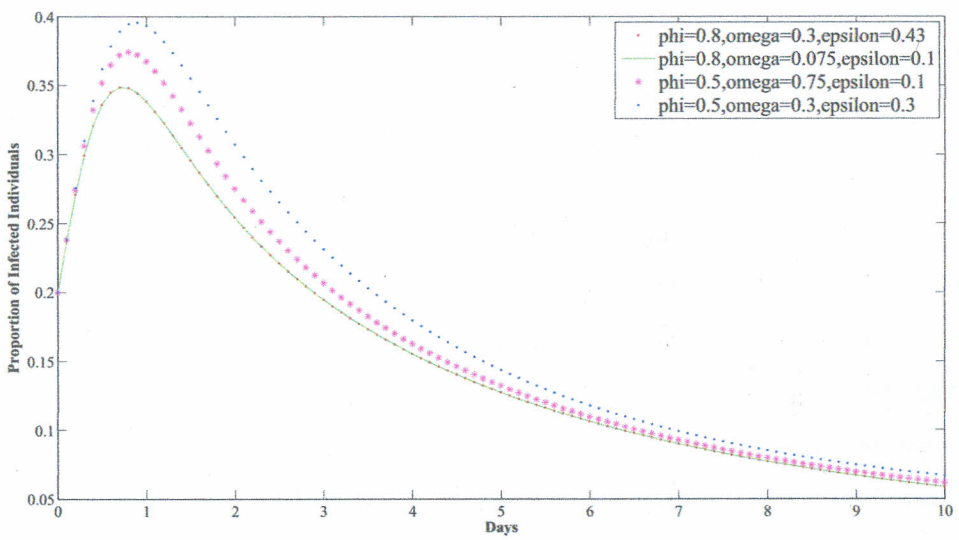


Figure 4.13: Effect of the Vaccination parameters on Infected class

The results in Figure 4.13 show the effect of varying vaccination parameters on the proportion of the infected individuals. The two lower curves (whose $\phi = 0.8$) are almost the same over the 10 days regardless of the variations in the values of $\epsilon$ and $\omega$. This result indicates that the strategy with a higher impact is by considering increasing the percentage of vaccination uptake.

## 4.5 Discussion

A quantitative analysis can be performed by using single-point estimates (referred to as deterministic). Using this method, one may assign values for discrete parameters to see what outcome they might have on the basic reproduction number from each. For example, what parameter values will result to a basic reproduction number of 1, less than 1 or more than 1. However, the approach considers only a few discrete outcomes, ignoring hundreds or thousands of others. It also gives equal weight to each outcome. That is, no attempt is made to assess the likelihood of each outcome. Monte Carlo simulation is a better way of addressing the drawbacks where uncertain inputs in a model (basic reproduction number) are represented using ranges of possible values of known (or assumed) probability distributions. Probability distributions are a much more realistic way of describing uncertainty in parameters used in computing the basic reproduction number. Fitting the probability distributions provide more information that may not be available when discrete values are used and hence improves the results. This explains the difference in Table 4.3 (probabilities computed from the simulated data) and Table 4.8(probabilities computed from the fitted probability distribution).

The results indicate that using the two strategies, there is a possibility of reducing the disease burden significantly. The expression in (4.12) clearly indicates that $R_\phi < R_o$ that is, when vaccination is used, the basic reproduction number is less than the basic reproduction number when vaccination is not used. The critical values for the proportion of the Streptococcus strain to be covered in the vaccine and vaccination

coverage in order to keep the basic reproduction number below 1 is also determine in the mathematical analysis. We then perform 10,000 replicates for all the vaccination and treatment strategies and thus obtain values of $R_\phi$ and $R_\tau$ , making it possible to find the probability of an epidemic. The probability distribution of $R_\phi$ and $R_\tau$ for the disease transmission rate is thus approximated to obtain the empirical percentage when $R_\phi$ and $R_\tau$ are less than 1. The empirical probability values in Table 4.3 indicate that there is 0.72% chance that there would be no outbreak if vaccination is used but 0% chance if treatment alone is used. This is also supported by the results from the analysis of variance which indicated that all the vaccination parameters and their interactions were highly significant in influencing the value of the $R_\phi$.

# Chapter 5

# ROLE OF CASE DETECTION IN A PNEUMONIA DYNAMICS

## 5.1 Introduction

Case detection strategy is an important step in controlling any disease within a population. A high case detection rate increases the expected effect of control program of disease epidemiology (Borgdorff, 2004). However, there are many undetected cases of pneumonia in the developing countries making it difficult to control pneumonia in a population despite efforts put in place. In this model therefore, we explain the quantitative impact of case detection in the transmission dynamics of pneumonia. Case detection involves prompt identification of pneumonia infected individuals using recommended methods of clinical diagnosis. These include; recognizing patterns of the disease and considering all possible diagnosis by physician, follow up of the individuals under treatment, communicating the test results in time, accurate data gathering, information processing, verifying any test results and gathering new data. Any delay or flaws of these practices can lead to undetected cases and results in inappropriate and/or inadequate treatment (Schiffman & Melissa, 2010).

## 5.2 Model Description and Formulation

This model has five compartments in total and is referred to as $S - I_1 - I_2 - C - R$ model. We denote S as individuals susceptible to the disease; C denotes those who are carriers of *Streptococcus pneumonia*, these individuals are infected with the bacteria but are yet to develop pneumonia(asymptomatic); $I_1$ denotes individuals who are infected and are unaware of their pneumonia status and $I_2$ are infected individual who

know their pneumonia status after being detected and are on treatment; recovered R(t), are those who were previously infected and "successfully" treated. The total population size is N , given by

$$N(t) = S(t) + C(t) + I_1(t) + I_2(t) + R(t) \tag{5.1}$$

Individuals enters class S(t) at a constant rate of $\nu$ through birth or immigration. The susceptible group get infected by the bacteria at a time dependent rate of $\lambda(t)$ given by

$$\lambda(t) = \psi \frac{\epsilon C(t) + I_1(t))}{N(t)} \tag{5.2}$$

where $\psi = \kappa \mathcal{P}$ is the effective contact rate and $\epsilon \leq 1$ account for the relative infectiousness of individuals in the Carriers (C) class in comparison to those in the undetected infectious ($I_1$ ) class. We assume that the infected individual ($I_2$)who already knoe their status are on treatment and cannot infect others. Individuals in all the compartments experience natural death at a constant rate $\mu$. A proportion $\rho$ of the newly infected individuals become carriers and move to class C , while the remaining proportion of the infected $(1-\rho)$ develop pneumonia and shows symptoms, they progress into the $I_1$ class. Since we are considering one carrier class and two infectious classes, it is important to note that we use the a two way paths $\rho$ and $(1-\rho)$. The carriers can develop disease symptoms and become symptomatically infectious at a rate $\pi$ when colonization takes place (McKenzie, 1999) or recover to gain immunity against the bacteria at an average rate $\beta$. The case detection rate of individuals in $I_1$ is denoted by $\xi$. Once a case is detected they progress to $I_2$ Class. Individuals in $I_2$ are treated at a rate $\eta$, however the recovery is dependent on the efficacy of the therapeutic treatment in this case denoted by $q$. We assume that treated individuals will leave the $I_2$ class and $q$ of them progress to $R$ while $1-q$ progressing to carrier class. Individuals in $I_1$ and $I_2$ can succumb due to the disease at the rate of $\alpha$. The parameters described here are summarized in Table 5.1. We then generate the systems of differential equations for the model as in (5.3) while the corresponding schematic diagram is shown in Figure 5.4

Table 5.1: Description of parameter used in the pneumonia model with case detection

| Parameter | Description |
|---|---|
| $\nu$ | Recruitment rate into the susceptible class |
| $\lambda$ | Force of infection due to Carriers |
| $\rho$ | Probability of a newly infected individual being a Carrier |
| $\pi$ | Rate at which Carriers become symptomatically infectious |
| $\eta$ | Rate or recovery from the symptomatically infection through treatment |
| $q$ | Treatment efficacy. |
| $\alpha$ | Per capita disease-induced death rate |
| $\delta$ | Per capita rate of loss of immunity |
| $\mu$ | Per capita birth rate |
| $\beta$ | Recovery rate of carriers and gaining partial immunity |
| $\xi$ | Case detection rate |

The above definitions and assumptions lead to the set of ordinary differential equations in (5.3);

$$\left.\begin{aligned}
\frac{dS(t)}{dt} &= \nu + \delta R(t) - (\lambda + \mu)S(t) \\
\frac{dI_1(t)}{dt} &= (1-\rho)\lambda S(t) + \pi C(t) - (\xi + \mu + \alpha)I_1(t) \\
\frac{dI_2(t)}{dt} &= \xi I_1(t) - (\eta + \mu)I_2(t) \\
\frac{dC(t)}{dt} &= \rho\lambda S(t) + (1-q)\eta I_2(t) - (\mu + \pi + \beta)C(t) \\
\frac{dR(t)}{dt} &= q\eta I_2(t) + \beta C(t) - (\mu + \delta)R(t)
\end{aligned}\right\} \tag{5.3}$$

### 5.2.1 Basic properties

From (5.2)and (5.3), it is easily shown that $\lim_{t\to\infty} N(t) \leq \frac{\nu}{\mu}$. Because model (5.3) monitors the dynamics of human populations, we assume that all state variable and parameters are more than or equal to zero for any time $t \geq 0$.

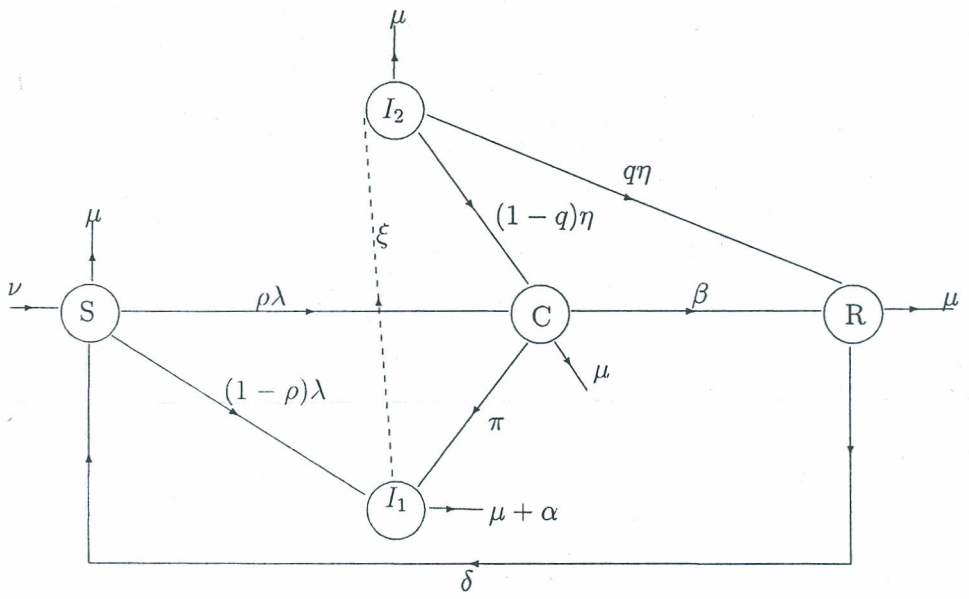


Figure 5.1: Proposed Compartmental pneumonia model with case detection

**Lemma 5.2.1** *The closed set* $\Gamma = \{(S, I_1, I_2, C, R) \in \mathbb{R}^5_+ : N(t) \leq \frac{\nu}{\mu}\}$ *is positively invariant with respect to model (5.3).*

**Proof** The rate of change of the total population, obtained by adding all the equations in the model (5.3)is given by

$$\frac{dN(t)}{dt} = \nu - \alpha I_1(t) - \mu N(t) \tag{5.4}$$

Since $\alpha I_1 \geq 0$, the solution of Equation (5.4) is

$$N(t) \leq \frac{\nu}{\mu} + \left(N(0) - \frac{\nu}{\mu}\right) e^{-\mu t} \tag{5.5}$$

It follows closely that for $N(0) \leq \frac{\nu}{\mu}$, $N(t) \leq \frac{\nu}{\mu}$ for all $t > 0$. Therefore all solutions of the model with initial conditions in $\Gamma$ remain in $\Gamma$ for all $t > 0$. Thus region $\Gamma$ is positively variant with respect to model (5.3)

## 5.3 Analysis of the pneumonia model with case detection

The model for pneumonia transmission with case detection is analyzed to determine the role of case detection in the transmission dynamics.We reduce the the system by using fraction of the state variables instead of the populations.

Let $s = \frac{S(t)}{N(t)}$, $f = \frac{I_1(t)}{N(t)}$,$e = \frac{I_2(t)}{N(t)}$,$g = \frac{C(t)}{N(t)}$ and $r = \frac{R(t)}{N(t)}$ such that $s + f + e + g + r = 1$. By differentiating the fractions with respect to time and simplifying, then (5.3) is rewritten as;

$$\left.\begin{aligned}
\frac{ds}{dt} &= \frac{(1-s)\nu}{N} + \delta r - \psi \epsilon g s - \psi f s + \alpha f s \\
\frac{df}{dt} &= (1-\rho)(\psi \epsilon g s + \psi f s) + \pi g - \left(\xi + \alpha + \frac{\nu}{N}\right) f + \alpha f^2 \\
\frac{de}{dt} &= \xi f - \left(\eta + \frac{\nu}{N}\right) e + \alpha f e \\
\frac{dg}{dt} &= \rho s \psi (\epsilon g + f) + (1-q)\eta e - \left(\pi + \beta + \frac{\nu}{N}\right) g + g\alpha f \\
\frac{dr}{dt} &= q\eta e + \beta g - \left(\frac{\nu}{N} + \delta\right) r + r\alpha f
\end{aligned}\right\} \quad (5.6)$$

### 5.3.1 Disease-free equilibrium and reproduction number

To determine the equilibrium points we equate (5.6) to zero as:

$$\left.\begin{aligned}
0 &= \frac{(1-s)\nu}{N} + \delta r - \psi \epsilon g s - \psi f s + \alpha f s \\
0 &= (1-\rho)(\psi \epsilon g s + \psi f s) + \pi g - \left(\xi + \alpha + \frac{\nu}{N}\right) f - \alpha f^2 \\
0 &= \xi f - \left(\eta + \frac{\nu}{N}\right) e + \alpha f e \\
0 &= \rho s \psi (\epsilon g + f) + (1-q)\eta e - \left(\pi + \beta + \frac{\nu}{N}\right) g + g\alpha f \\
0 &= q\eta e + \beta g - \left(\frac{\nu}{N} + \delta\right) r + r\alpha f
\end{aligned}\right\} \quad (5.7)$$

At steady state, we use $\frac{\nu}{N} = \mu + \alpha f$ to substitute into each of the equations in (5.7) and reducing it to;

$$\left.\begin{aligned} &\mu + \alpha f - \nu s + \delta r - \psi \epsilon g s - \psi f s = 0 \\ &\psi \epsilon g s + \psi f s - \psi s \rho \epsilon g - \psi s \rho f + \pi g - \xi f - f\mu - \alpha f = 0 \\ &\xi f - e\eta - e\mu = 0 \\ &\psi s \rho \epsilon g + \psi s \rho f + e\eta - q\eta e - g\mu - \pi g - \beta g = 0 \\ &q\eta e + \beta g - r\mu - \delta r = 0 \end{aligned}\right\} \tag{5.8}$$

using $r = \frac{q\eta\xi f + \beta g\eta + \beta g\mu}{(\eta+\mu)(\mu+\delta)}$, $e = \frac{\xi f}{\eta+\mu}$ and s=1-e-f-r-g, we reduce (5.8) to:

$$\left.\begin{aligned} &\psi \epsilon g s + \psi f s - \psi s \rho \epsilon g - \psi s \rho f + \pi g - \xi f - f\mu - \alpha f = 0 \\ &\psi s \rho \epsilon g + \psi s \rho f + e\eta - q\eta e - g\mu - \pi g - \beta g = 0 \end{aligned}\right\} \tag{5.9}$$

whose Jacobian Matrix is is given by:

$$J = \begin{bmatrix} \psi s - \xi - \mu - \alpha - \psi s \rho & \psi \epsilon s + \pi - \psi s \rho \epsilon \\ \psi s \rho & \psi s \rho \epsilon - \mu - \pi - \beta \end{bmatrix} \tag{5.10}$$

Let $R_o$,the basic reproduction number,be the expected number of new infections created by an infected individual under the most favorable conditions for transmission. Then for Model (5.6),we compute the basic reproduction number as

$$R_o = \psi \left( \frac{(1-\rho)\left((1-q)\eta\epsilon\xi + B(\eta+\mu)\right)}{A(\eta+\mu)B - \pi\eta\xi(1-q)} + \frac{\rho(\eta+\mu)(\pi+\epsilon A)}{A(\eta+\mu)B - \pi\eta\xi(1-q)} \right) \tag{5.11}$$

where, $A = \xi + \mu + \alpha$ and $B = \mu + \pi + \beta$

The numerator of (5.11) represent the rate of inflow into the diseased classes ($I_1, I_2$ and $C$) while the denominator represent the rate of outflow from the diseased classes. In general,for any disease in any host population,the disease can become an epidemic only if $R_o > 1$. The mathematical condition $R_o > 1$ can be intuitively interpreted as saying that there exist some conditions under which the disease can grow. On the sensitivity analysis of $R_o$ with respect to the rate of case detection (CDR), we find

the limit of $R_o$ and CDR tends to infinity and when it tends to zero as shown below.

$$\lim_{\xi \to \infty} R_o = -\frac{(1-\rho)\psi\,\epsilon}{\pi} < 0 \tag{5.12}$$

$$\lim_{\xi \to 0} R_o = \frac{(1-\rho)\psi\,(\mu+\pi+\beta) + \psi\,\rho\,\pi + \psi\,\rho\,\epsilon\,(\xi+\mu+\alpha)}{(\xi+\mu+\alpha)(\mu+\pi+\beta)} \tag{5.13}$$

The results in (5.12) shows that when the CDR tends to infinity, the $R_o$ tends to negative side making it impossible for disease transmission. On the other hand, when the CDR tends to zero, the $R_o$ tends to positive side and the disease is likely to invade the population if the right hand side of (5.13)is more than 1.

Disease-free equilibrium point is a steady-state solution where there is no disease. Here we define the *"diseased"* classes as the infected individuals that are already detected or not detected. We denote the disease-free equilibrium point by $E_o = S_o, I_{1o}, I_{2o}, T_o, R_o$. When the system is at disease-free, the diseased classes are all equal to zero. Hence disease-free equilibrium point $E_o$ is given by;

$$E_o = \left\{\frac{\nu}{\mu}, 0, 0, 0, 0\right\} \tag{5.14}$$

**Stability of the disease-free equilibrium. ($E_o$)**

To examine the local stability of the disease-free equilibrium $E_o$ we evaluate the Jacobian matrix (5.10)at $E_o = \left\{\frac{\nu}{\mu}, 0, 0, 0, 0\right\}$ is

$$J(E_o) = \begin{bmatrix} \frac{\psi\,\nu}{\mu} - \xi - \mu - \alpha - \frac{\psi\,\nu\,\rho}{\mu} & \frac{\psi\,\epsilon\,\nu}{\mu} + \pi - \frac{\psi\,\nu\,\rho\,\epsilon}{\mu} \\ \frac{\psi\,\nu\,\rho}{\mu} & \frac{\psi\,\nu\,\rho\,\epsilon}{\mu} - \mu - \pi - \beta \end{bmatrix} \tag{5.15}$$

The eigenvalues for $J(E_o)$ are computed as

$$\lambda_1 = \lambda_2 = \frac{\psi\nu(1-\rho(1-\epsilon))}{\mu} - (\mu+\xi+\alpha)\frac{\psi\nu(1-\rho(1-\epsilon))}{\mu} - (\mu+\xi+\alpha) \tag{5.16}$$

Note that in (5.16), $\frac{\psi\nu(1-\rho(1-\epsilon))}{\mu}$ is a proxy of the inflow into a diseased class while $(\mu+\xi+\alpha)$ represents a outflow from a diseased class.

**Proposition 5.3.1** *The disease-free equilibrium $E_o$ is locally asymptotically stable if $R_o < 1$ and unstable if $R_o > 1$.*

**Proof** To show the stability of the system, we need to show that the two eigenvalues of $J(E_o)$; are negative if $R_o < 1$.

If $R_o < 1$, then the numerator of (5.11) (the rate of inflow into the diseased classes) is less than the denominator (the rate of outflow from the diseased classes). This means that from (5.16), $\frac{\psi\nu(1-\rho(1-\epsilon))}{\mu} < (\mu+\xi+\alpha)$, making all the real part of the eigenvalues in (5.16) negative hence the disease-free $E_o$ equilibrium is locally asymptotically stable

**Theorem 5.3.2** *The disease-free $E_o$ equilibrium is globally asymptotically stable if $R_o < 1$.*

**Proof** Let,

$L(f,g) = f^2 + g^2$, then,

Then L is positive definite and the time derivative of L is computed as shown below.

$L' = \frac{dL}{df}\frac{df}{dt} + \frac{dL}{dg}\frac{dg}{dt}$

$$L' = [\psi\,(\epsilon\,g+f)\,s\,((1-\rho)\,f+g\rho)+f\pi\,g+ge\eta\,(1-q)]-[g^2\,(\mu+\pi+\beta)+f^2\,(\xi+\mu+\alpha)] \tag{5.17}$$

If $R_o < 1$, then the numerator of (5.11) (the rate of inflow into the diseased classes) is less than the denominator (the rate of outflow from the diseased classes) implies that in (5.17), $\psi\,(\epsilon\,g+f)\,s\,((1-\rho)\,f+g\rho)+f\pi\,g+ge\eta\,(1-q) < g^2\,(\mu+\pi+\beta)+f^2\,(\xi+\mu+\alpha)$ hence, $L' < 0$. We therefore conclude that $E_o$ is globally asymptotically stable in the interior of $\Gamma$.

**Stability of the endemic equilibrium. ($E^*$)**

We show the global stability of the endemic equilibrium, ($E^* = (s^*, f^*, e^*, g^*, r^*)$ by using the jacobian matrix ;

$$J(E^*) = \begin{bmatrix} \psi s^* - \xi - \mu - \alpha - \psi s^* \rho & \psi \epsilon s^* + \pi - \psi s^* \rho \epsilon \\ \psi s^* \rho & \psi s^* \rho \epsilon - \mu - \pi - \beta \end{bmatrix} \tag{5.18}$$

**Theorem 5.3.3** *The endemic Equilibrium, $E^*$ of the System (5.3) is stable if $R_o > 1$ and unstable if $R_o < 1$.*

**Proof** Consider the Jacobian matrix $J(E^*)$, its trace and determinant are computed as;

$$Trace(J(E^*)) = \psi s (1 - \rho + \epsilon \rho) - (\xi + 2\mu + \alpha + \pi + \beta) \tag{5.19}$$

$$Det(J(E^*)) = -(\psi s ((1 - \rho)(\mu + \beta) + \pi + \epsilon \rho (\xi + \mu + \alpha)) - (\xi + \mu + \alpha)(\mu + \beta + \pi)) \tag{5.20}$$

If $R_o > 1$, then the numerator of (5.11) (the rate of inflow into the diseased classes) is more than the denominator (the rate of outflow from the diseased classes) implies that from(5.19) and (5.20) $Trace(J(E^*)) > 0$ and $Det(J(E^*)) < 0$ hence $E^*$ is unstable.

## 5.4 Numerical Simulations

To observe the role played by case detection in transmission dynamics of pneumonia transmission over time, numerical simulations were done using MAPLE 16.0 and MATLAB (mathematical simulation packages). We use parameters values shown in Table (5.2) for simulation. These parameters have been derived from epidemiological literature and WHO while other parameters have been allowed to vary within the possible intervals.

Table 5.2: Parameter Value used in the pneumonia model with case detection

| Parameter | Value | Source |
|---|---|---|
| $\nu$ | $\mu N_0$ | (Doura et al., 2000) |
| $\kappa$ | 1-10 per day | Estimated |
| $\mathcal{P}$ | 0.89 to 0.99 | (Doura et al., 2000) |
| $\psi$ | $\kappa\mathcal{P}$ | Expressed as in (3.2) |
| $\epsilon$ | 0.001124 | (Doura et al., 2000) |
| $\rho$ | 0.338 | (Kateete et al., 2012; Kimura et al., 1984) |
| $\pi$ | 0.00274 to 0.01096 per day | (Doura et al., 2000) |
| $\eta$ | 0.0238 to 0.0476 per day | (Thadani, 2011) |
| $q$ | 0.1 to 1 | (Doura et al., 2000) |
| $\alpha$ | 0.33 | Estimated |
| $\delta$ | 0.2 | Estimated |
| $\mu$ | 0.0002 per day | (World Health Organization, 2010) |
| $\beta$ | 0.0115 | (Hill et al., 2008) |
| $\xi$ | 0.80 | Estimated |

### 5.4.1 Simulations to illustrate the equilibrium of the system

Using the parameter values in Table 5.2, we carried out numerical simulations of (5.3) to asses the equilibrium of the system. The simulation results are depicted in Figure 5.2.The results shows a sharp decrease in susceptible individuals corresponding to the an increase of the corresponding infected(detected and undetected cases) during the initial stage of the epidemic. The undetected cases increases in small percentage then decreases sharply to a steady state point. The phase portrait in Figure 5.2 (b) is obtained by different initial values. It illustrates that for varying initial conditions, the model solutions converge at a steady state point. This confirms the steady state solutions in the analysis.

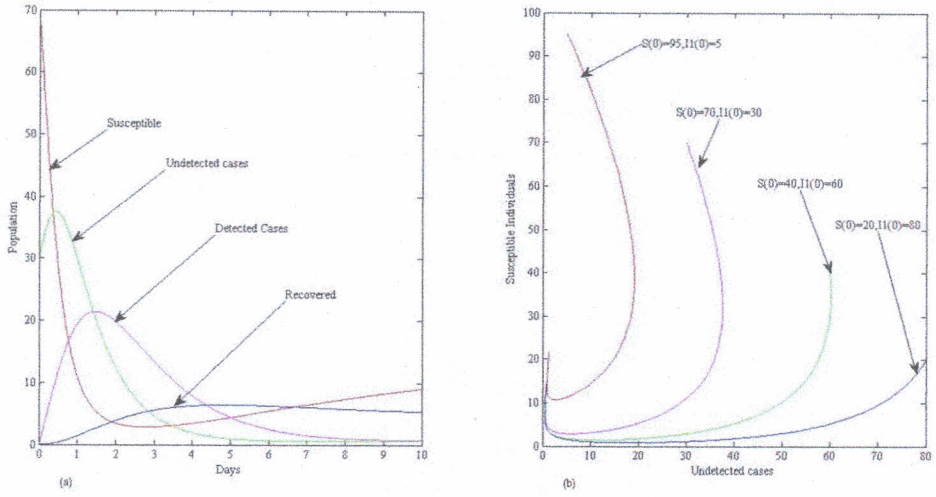


Figure 5.2: Population dynamics of the pneumonia model with case detection

### 5.4.2 Effect of case detection rate on the Basic reproduction number ($R_o$)

The mathematical analysis results in (5.12) shows the role played by case detection rate on the basic reproduction number. The simulation results in Figure 5.3 confirms the mathematical results that, an increase in the case detection rate reduces the basic reproduction number hence the chance of new infections reduced.

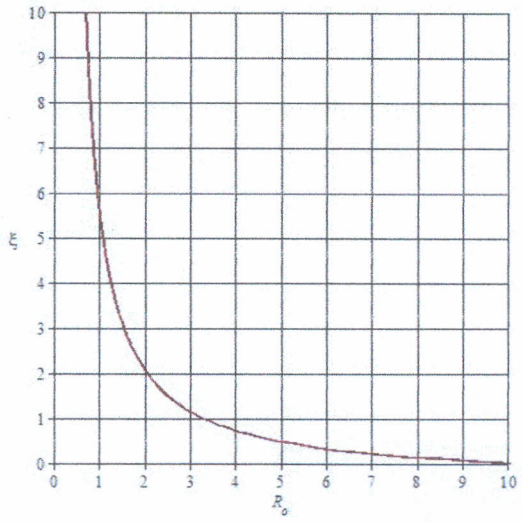


Figure 5.3: Effect of case detection on $R_o$

### 5.4.3 Role of case detection in the absence of treatment

Simulation results in Figure (5.4) shows a graphical representation of the impact case detection of infected individuals on pneumonia transmission dynamics in the absence of treatment ($\eta \simeq 0$).The graphs suggest that pneumonia case detection have some partial positive degree in the control of the disease as noted by a small rate of reduction in the susceptible class and a small rate of increase in the recovered class as case detection rates are increased. The incidence rate of the undetected cases is also reduced when the CDR is increased.

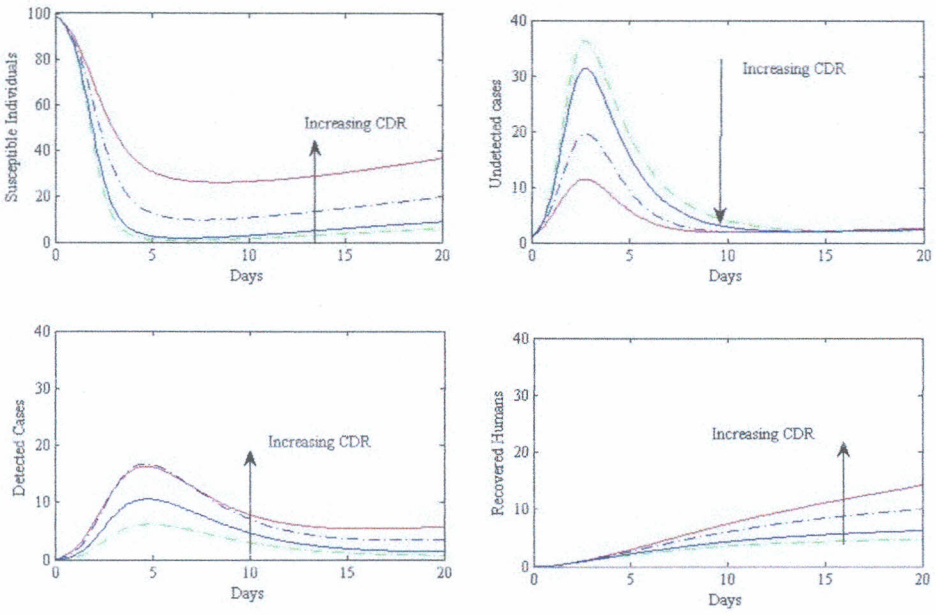


Figure 5.4: Effects of varying pneumonia case detection rate in the absence of treatment $\eta \simeq 0$. The direction of arrow shows the increase in case detection rate (CDR).

### 5.4.4 Role of case detection in the presence of treatment

Next, we illustrate the effect case detection on pneumonia transmission dynamics when it is accompanied with a treatment (this is shown in Figure 5.5). The graph indicates that increasing the treatment rate with any case detection rate reduces the rate of reduction in susceptible class, reduces the rate of increase of the undetected cases and increases the rate of recovery.

## 5.5 Discussion

It is evident that an increase in the rate of case detection decreases the basic reproduction number, means a reduction of disease incidence. These results are confirmed

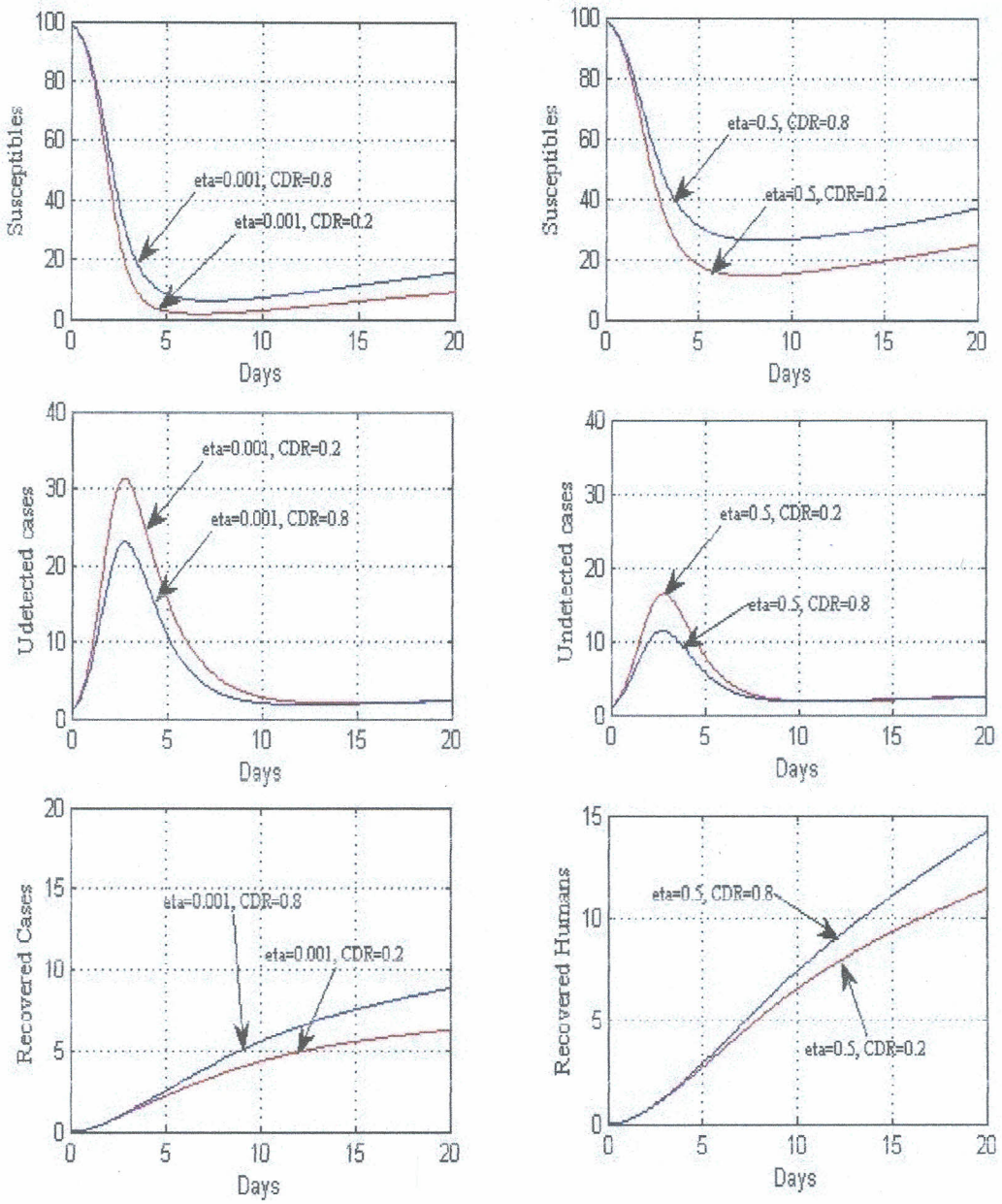


Figure 5.5: Effects of varying pneumonia case detection rate with different rates of treatment $\eta = 0.001$ and $\eta = 0.5$

in the simulation above that case detection is a necessary step towards reducing the disease burden, however when accompanied by adequate measures such as treatment, then the disease incidence is reduced further. As much as the high rate of case detection reducing the burden of the disease, when incorporated with effective treatment, the burden of the disease will be reduced more.

# Chapter 6

# CONCLUSION, RECOMMENDATION AND FURTHER RESEARCH

## 6.1 Conclusion

We have constructed 3 models for pneumonia dynamics: a basic model without considering any particular control strategy, a model with vaccination and treatment as control strategies and a model with case detection. All the models are analyzed mathematically and simulated using parameters obtained from biological literature. We have structured our conclusion based on the specific objectives that were stated earlier and results discussed above.

### 6.1.1 Objective 1:To determine the conditions necessary for controlling/ reducing pneumonia transmission by analyzing basic pneumonia model.

This objective aimed at providing information on the optimal approach of controlling pneumonia and it is addressed using the model represented by system (3.1). The results from the analysis showed that the presence of carriers may hinder the disease eradication if not addressed. Efforts to reduce the burden of diseases with carriers is hard due to their contributions to the transmission dynamics. Carriers do not show symptoms and therefore they sometimes go un-noticed. We conclude that, applying strategies that can create awareness of carrier status will have a much greater impact in reducing the disease burden than concentrating on reducing the infected population alone. This is in agreement with the studies done earlier by Agarwal & Verma (2012) and Kalajdzievska & Li (2011). A strong significant positive correlation exist between

the carrier-infected interaction (infected individuals joining carrier population and vice versa) and disease prevalence.

### 6.1.2 Objective 2: To determine the optimal vaccination and treatments strategies on pneumonia transmission dynamics using the probability distributions of the basic reproduction number.

Two control strategies viz; vaccination and treatment were assessed using the second model presented in (4.1) to address this objective. The two strategies are the most common disease control strategies used in controlling many diseases. From the analysis and simulation of the model we can conclude that the use of vaccination reduces the disease prevalence at a greater percentage. This is confirmed by earlier research by Matt et al. (2013), however the use of treatment alone was not significant. Computing the probability density functions of the reproduction number provides an opportunity of computing a likelihood of the disease outbreak. The density functions of the basic reproduction numbers (when treatment and vaccinations are used) are all skewed to the right which is a clear indication that there is more likely to have the value of the Basic reproduction number reduced below 1 when control strategies are used.

### 6.1.3 Objective 3: To evaluate the impact of case detection of pneumonia on its transmission dynamics.

The case detection strategy is a potential and effective control strategy for pneumonia in a community. The decreasing trend of $R_o$ with an increasing value of the case detection rate as described in (5.13) and a confirmation in the simulation shown in Figure 5.4 implies that case detection plays an important role in reducing the disease incidence. Through simulation, we have also computed the critical value for the case detection rate and concluded that detecting at least 57% of the cases guarantees the

no new infection. The results that we obtain here are in conformity to that obtained in a study on case detection of TB by Styblo (1991).

## 6.2 Recommendation

Based on the conclusions described in the section above, it is recommended that to prevent future outbreaks or to reduce the prevalence of pneumonia, major effort/strategy should target reducing the proportion of the carriers of *Streptococcus Pneumoniae* from the population since this is the state that can always transmit the disease without being noticed or being aware of their status. Sometimes it might not be practical to reduce the proportion of the carriers (Kalajdzievska & Li, 2011). Many people, pick up diseases from the people they interact with such as in school, at work stations, in healthcare facilities etc amplifying disease transmission where one initial case can either lead to several more cases within a population. It would be possible to do this by reducing the number of contacts as possible.

A vaccination strategy is more significant in controlling the disease prevalence. The expression in (??) implies that the critical value for the minimum proportion of the serotype to be covered in a vaccine should be 22% for a guaranteed efficiency of the vaccination strategy. On the other hand the expression in (4.15) suggests that a vaccination coverage of at least 54% would guarantee efficiency in vaccination strategy. We also recommend that case detection to be included whenever practicable in the control strategy of pneumonia in a population.

## 6.3 Further Research

In this study we constructed and analyzed three models with each having specific assumptions. The modeling techniques that was used here was basically deterministic

modeling approach. However in the second model, we introduced the probabilistic simulation of the basic reproduction number. The probabilistic approach or stochastic modeling takes into consideration random effect and therefore can give true picture by identifying any hidden variations in the disease transmission dynamic. A further research of pneumonia transmission dynamics using probabilistic approach will give more insight of the disease dynamics.

Studies have shown that there is some correlation between pneumonia incidence and environmental conditions and socio-economics status of the population, however we did not consider them in this study. It would be interesting to construct models that incorporate both environmental and socio-economic influence so as to measure their effect on the transmission dynamics.

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