MODELLING THE ROLE OF REHYDRATION AND ANTIBIOTIC TREATMENT ON REDUCTION OF CHOLERA MORTALITY

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A research thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Applied Mathematics of Masinde Muliro University of Science and Technology.

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DECLARATION

This research thesis is my original work prepared with no other than the indicated sources and support and has not been presented elsewhere for a degree or any other award.

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APPROVAL

We the undersigned certify that we have read and hereby recommend for acceptance of Masinde Muliro University of Science and Technology a research thesis entitled "Modelling the Role of Rehydration and Antibiotic Treatment on Reduction of Cholera Mortality".

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DEDICATION

This work is dedicated entirely to my beloved Dad Hezron Saggia, my aunt Marry Saggia and my mother Eunice Owade.

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ABSTRACT

Cholera is an infection of the small intestine of humans caused by a gram-negative bacterium called *Vibrio cholerae* whose cell membrane thickness is small and stains pink when tested in the laboratory. It is spread through eating food or drinking water contaminated with faeces from an infected person. It causes rapid dehydration and general body imbalance, and can lead to death since untreated individuals suffer severely from diarrhea and vomiting. Its dynamics involves multiple interaction between the human host, the pathogen, and the environment which contributes to both human to human and indirect environment to human transmission pathways. When infected individuals move from one place to another, they also lead to an outbreak of cholera based on their lifestyle. Mathematical models of cholera transmission dynamics and protection measures such as vaccination, improved sanitation, water chlorination, and education have been formulated but did not assess the role of rehydration and antibiotic treatment. In this study we have formulated a mathematical model based on system of ordinary differential equations (ODE_s) to assess the role of rehydration and antibiotic treatment in reduction of cholera mortality. All solutions in our model are positive since we are dealing with human population, we have also shown that the solution of the model is bounded. Since the solution of the model is positive and bounded, hence the model is well posed. The basic reproduction number is derived using the Next Generation matrix approach and the existence of the steady states of the model are also determined. The disease free equilibrium is shown to be locally asymptotically stable and it's global stability has been shown to be globally stable using the Comparison Theorem. Endemic equilibrium has also been shown to be locally asymptotically stable. Numerical simulation of the model done using MATLAB software shows that rehydration and administration of antibiotics play a major role in reducing cholera deaths. The study will be relevant to planners and policy makers in health care system in facilitating prompt diagnosis and treatment of cholera.

ABBREVIATIONS

WHO - World Health Organization

MATLAB - Mathematical Laboratory

KEMRI - Kenya Medical Research Institute

DFE - Disease Free Equilibrium

EE - Endemic Equilibrium

CIA - Central Intelligence Agency

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CHAPTER 1

INTRODUCTION

1.1 Background information

Cholera is an infection of small intestine caused by a gram-negative bacterium called *Vibrio cholerae* whose cell membrane thickness is small and stains pink when tested in the laboratory. Blood stream infection has been noted for *Vibrio cholerae* $O141$ and $O1$ in which some cases were reported Gordon et' al[9]. In one of the cases, a male twin was born in Queen Elizabeth Central Hospital in Blantyre, Malawi in March 1998, at 34 weeks gestation. The child was well until day 2, when it became hypothermic, hypoglycemic and peripherally cyanosed. It had no diarrhoea. Blood culture was taken, treatment with penicilin and gentamicin was began and expressed breast milk was fed by nasogastric tube, but the child died 13 hours later. Blood culture was done and grew *Vibrio cholerae* $O1$ at 24 hours and stool culture was not taken. The second twin followed similar clinical course and died on day 2. Blood culture was negative. The mother had no diarrheal disease Jesudson et' al[12]. The dynamics of cholera involve multiple interactions between the human host, the pathogen, and the environment, which contribute to both human to human and indirect environment to human transmission pathways Mari et' al[15]. The bacterium is generally present in the faeces of an infected person for 7 to 14 days, though with treatment, the symptoms do not last long Mukandavire et' al[17]. The bacterium is acquired by humans through eating food or drinking water contaminated by faeces from an infected person. The incubation period of the bacteria is 12 hours to 5 days Mwasa et' al [16] . During infection the bacteria attach themselves to the intestinal walls where they multiply and produce toxic proteins which cause the intestines to secrete large amounts of fluids. Signs and symptoms of cholera infection include stomach cramps, mild fever, vomiting and watery diarrhoea often accompanied by

stomach pains which leads to dehydration as one can lose up to 1 litre of fluids per hour. If untreated severe dehydration will lead to death Nelson *et′ al* [18].

Diagnosis is done through culture of the stool, agglutination tests are then done for confirmation of the disease. Treatment is based on the severity of dehydration of the patient Sulayman *et′ al* [20]. Simple oral rehydration solutions containing salts and glucose are used to treat mild to moderate cases. For severe cases, treatment is based on antibiotics that can shorten the cause and diminish the severity of cholera, but it is important to replace the fluids that have been lost through diarrhea. To replace the lost fluids, rehydration solutions, containing a mixture of salts and sugar are mixed with water and drunk in large amounts as a result fatality rates are reduced to less than one percent Neil *et′ al* [19]. Antibiotics is used to treat in case it reaches a case of bloodstream infection in which the findings show that the use of antibiotics reduces volume of stool output by $8\% - 92\%$, duration of diarrhea by $50\% - 56\%$ and duration of positive bacterial culture by $26\% - 83\%$ World Health Organization[22]. The existence of acquired immunity against the cholera disease has been known since very ancient time. Patients recovering from *Vibrio cholerae* infection are either protected against reinfection with the same *Vibrio cholerae*, or the subsequent episodes are less severe Lavine *et′ al*[13]. Prevention and control measures of cholera include improved food safety, provision of safe drinking water, proper sanitation, and strengthening surveillance. Health education is also very important in raising public awareness on preventive measures Zhang *et′ al*[26].

Diarrhoeal diseases like cholera cause most global death in children under the age of five. It is estimated that cholera affects 3 - 5 million people and cause 100,000-130,000 deaths in the world annually World Health Organization[8]. The disease is more common in developing countries especially Africa such as Nigeria (2010), Zimbabwe (2008 - 2009), Kenya (2015) parts of Asia such as Vietnam (2009), Iraq

(2008) and South and Central America such as Haiti (2010) where there is inadequate sanitation and lack of clean water. In 2009 a total of $221,226$ cases with 4883 deaths were reported to the WHO with Africa accounting for 98% of the cases and 99% of the deaths CHC[3]. In Kenya for instance $5,564$ cases of cholera and 113 deaths were reported between $(2010-2014)$ World Health Organization[24]. Between (2014-2016) Cholera cases have been reported in Siaya, Garissa and Homabay counties in Kenya. Cholera deaths in Kenya is 6.8 deaths in every 1000 people in a given population in a year CIA[5]. By developing a mathematical model on the role of rehydration and antibiotic treatment we will therefore be able to understand how cholera mortality is reduced.

1.2 Statement of the problem

Many control programmes have been set up to promote effective prevention of cholera such as creating awareness through education. However, cholera has remained persistently endemic which is frequently punctuated by severe outbreaks in urban and rural areas with consequences of high mortalities. These cases are often aggravated by the chaos of war and upsurge of slums in urban areas. Cholera deaths are attributed to rapid dehydration and lack of timely administration of antibiotics. Several mathematical models on transmission dynamics and control of cholera have been formulated but none that assesses both rehydration and antibiotic treatment has ever been developed. As a result this study will assess the role of rehydration and antibiotic treatment on reduction of cholera mortality.

1.3 Objectives of the study

1.3.1 General Objective

The main objective of this study is to assess the role of rehydration and antibiotic treatment on the reduction of cholera mortality.

1.3.2 Specific Objective

The specific objectives of this study are:

(i)To formulate a system of ODEs to assess the role of rehydration and antibiotic treatment on reduction of cholera mortality.

(ii)To perform stability analysis of the model formulated with respect to the basic reproduction number derived using the Next Generation Matrix approach.

(iii)To assess the role of rehydration and antibiotic treatment in the model by means of simulation using MATLAB software.

1.4 Justification of the Study

Cholera outbreaks have attracted global attention due to high cases of cholera mortality attributed to dehydration. Cholera deaths are presently reduced through rehydration and administering antibiotics to the infected individuals. We therefore aim to better the understanding of how rehydration and antibiotics treatment help in reducing cholera mortalities so as to gain useful guidelines on how cholera patients can be treated in good time. This is because cases of cholera deaths have been reported after administration of Oral Rehydration Solutions when the bacteria has reached the bloodstream level.

1.5 Significance of the Study

Mathematical modeling of cholera is a valuable component for public health planning and response. By developing and analyzing a mathematical model to investigate the role of rehydration and antibiotic treatment, the study will be relevant in planning and decision making among stake-holders in the health system who are responsible for equipping public health facilities that can be used to test for cholera in KEMRI and provide medicine to treat cholera patients in good time.

1.6 Methods

In this study, a cholera model is developed to assess the role of rehydration and antibiotic use in reduction of cholera mortality. The existence of the steady states of the model is determined. Stability analysis of the steady states is also determined with respect to the basic reproduction number, derived using the next generation matrix approach. MATLAB software is also used to carry out numerical simulation to graphically illustrate the role played by rehydration and antibiotic use in reducing cholera deaths.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Bloodstream infection has been noted for *Vibrio cholerae* $O141$ and $O1$ Gordon et' al[9]. Untreated individuals suffer severely from diarrhea and vomiting. It can cause a rapid dehydration and general body imbalance, and can lead to death. As a water/food borne disease, cholera is typically transmitted through pathogen ingestion, such as drinking sewage-contaminated water, or eating food prepared by an individual with contaminated hands. Meanwhile, different transmission pathways are possible.

Prevention and control measures of cholera include improved food safety, provision of safe drinking water, proper sanitation,strengthening surveillance, health education, rehydration and use of antibiotics Colwel[6].

Cholera is an ancient disease that continues to cause epidemic and pandemic infections despite ongoing efforts to limit its spread Gosh et' al[10]. The existence of acquired immunity against the cholera disease has been known since very ancient time. Patients recovering from *Vibrio cholerae* infection are either protected against reinfection with the same *Vibrio cholerae*, or the subsequent episodes are less severe Lavine et' al[13]. The last few years have witnessed many cholera outbreaks in developing countries, including India(2007), Congo(2008), Iraq(2008), Zimbabwe(2008-2009), Vietnam(2009), Nigeria(2010), Haiti(2010) and Kenya(2014-2015). In the year of 2010 alone, it is estimated that cholera affected 3-5 million people and caused 100,000-130,000 deaths in the world World Health Orgaization[24]. Particularly, cholera represents a significant public health burden to developing countries and cholera continues receiving worldwide attention World Health Organization[24]. This study seeks to assess role of rehydration and antibiotic treatment on reduction

of cholera mortality.

2.2 Cholera Models

Several mathematical cholera models have been formulated and analyzed. Emmanuel *et' al*. [7] formulated an SIR-C cholera model to study the dynamics of cholera with control strategy where C denotes the pathogen concentration. Based on their idea, cholera deaths can be reduced by good sanitation and water treatment. Other control strategies like vaccination and curative treatment were not considered in the model.

Aryda *et' al*[1] developed and analyzed an SIR model to investigate cholera disease with education and chlorination. They established that with no chlorination, the disease free equilibrium is shown to be globally stable and the sensitivity analysis of basic reproduction number shows that it is most sensitive to education, per capita birth and death rate of the bacteria. They also concluded that per capita birth and death rate of the bacteria can be increased by water chlorination. The model ignored factors such as environmental factors which may promote disease outbreak among poor communities. The model also ignored the role of rehydration and antibiotic treatment.

Wang and Modnak [23] developed an SIR model using systems of ordinary differential equations to study the dynamics of cholera. The protection measures such as vaccination, eating well cooked food, water chlorination and good sanitation were incorporated. The model also represents coupling between the multiple transmission pathways and the control measures. Their stability analysis shows that the basic reproduction number for the control model plays a crucial role in determining the epidemic and endemic dynamics. They concluded that vaccination and treatment closely interplay with each other and that combination of multiple intervention

methods generally achieves better results than a single control such as vaccination only. However, they have not specified the treatment.

The role of aquatic reservoir on the dynamics of cholera is investigated by Codeco[2]. This is done by use of an SIR model incorporating aquatic population of *Vibrio cholerae*. Three hypothetical communities are used to illustrate the dynamics, these are the endemic, epidemic and cholera free population. Qualitative results of the cholera free population shows that the disease can be minimized by preventing water contamination, drinking of treated water and by diluting cholera diarrhea using large quantities of water. The results of the model show that endemic cholera can be maintained even without permanent reservoirs, however, the analysis does not show how cholera mortality can be reduced through rehydration and antibiotic treatment. In his findings, the development of cholera modelling requires a better understanding of *Vibrio cholerae* ecology and epidemiology by knowing estimates of the parameters of *Vibrio cholerae* infection in endemic population as well as better description of the relationship between dose and virulence. The model does not incorporate measures such as rehydration and antibiotic treatment on reduction of cholera mortality.

A model to study the impact of human behaviour on cholera dynamics is developed by Xueying et' al[25]. They assumed that the population is well aware of the development and severity of the disease and individuals will be free from cholera bacteria through protection measures such as chlorination, good sanitation, education, eating well cooked food and improving on their human waste disposal will change the rate at which the disease spreads, the risk of infection in the environment and the epidemic and endemic levels.

These models do not show the role of rehydration and antibiotic treatment in reduction of cholera mortality. It is for this reason this study seeks to assess role of

rehydration and antibiotic treatment on reduction of cholera mortality.

CHAPTER 3

MODEL FORMULATION AND ANALYSIS

3.1 Introduction

In this section we develop a cholera model using systems of ordinary differential equations (ODEs) that classifies the human population $N(t)$ into classes of susceptible $S(t)$, infected $I(t)$ and recovered $R(t)$, where $I(t) = I_a + I_b$, I_a represents individuals infected with the bacteria in the intestine only and I_b represents individuals infected with bacteria in both the intestine and the bloodstream.

3.1.1 Assumptions of the Model

The model formulated is based on the following assumptions;

(i)Individuals recover with temporary immunity.

(ii)Bacteria shed rate is equal for both cases of infection.

(iii) Infected individuals only acquire the bacteria from the environment i.e there is no direct human to human transmission.

(iv)There is high death rate due to infection in both the intestine and the bloodstream

3.1.2 Description of variables and parameters

The parameters and state variables are defined as follows:

Table 3.1: Description of Parameters and Variables

Symbol	Desription
Λ	Human recruitment rate
S(t)	Susceptible population
I(t)	Infected population
R(t)	Recovered population
I_a	infected individuals in the intestine only
I_b	infected individuals in both the intestine and the bloodstream
μ	Human natural death rate
γ_1	human death rate due to infection in the intestine only
γ_2	human death rate due to infection in both the intestine and the bloodstream
σ_1	rate at which bacteria shed rate in the intestine reduces
σ_2	rate at which bacteria shed rate in the intestine and bloodstream reduces
δ_1	Recovery rate as a result of rehydration
δ_2	Recovery rate as a result of rehydration and administration of antibiotics
α	Effective contact rate of the bacteria
d_1	bacteria shed rate due to rehydration
d_2	bacteria shed rate due to rehydration and administration of antibiotics
μ_b	bacteria death rate
K	the carrying capacity of $Vibrio$
C	per capita growth rate of $Vibrio$
B	Population of $Vibrio$
$CB(1-\frac{B}{K})$	logistic growth rate of a the pathogen population
$\frac{B}{K+B}$	probability of susceptible to catch cholera
$[\frac{\alpha B}{K+B}]I_b$	Force of infection for the bacteria in both the intestine and the blodstream
$[\frac{\alpha B}{K+B}]I_a$	Force of infection for the bacteria in the intestine only

3.2 The Model Description

In our model, there is a decrease in human population through natural death at a rate μ or as a result of death due to infection either in the intestine only γ_1 or death due to infection in both the intestine and the bloodstream γ_2.

When rehydration is administered the bacteria shed rate as a result of the infection in the intestine only reduces at the rate σ_1 and the bacteria shed rate as a result of the infection in both the intestine and the bloodstream is reduced at the rate σ_2 due to rehydration and administration of antibiotics. Recovery rate as a result of rehydration is given by δ_1 and recovery rate due to rehydration and administration of antibiotics is given by δ_2 , B is the concentration of $Vibrio$ in the environment, K the carrying capacity of $Vibrio$ where K > 0.

The effective contact rate of the bacteria is given by α and the probability of susceptible to catch Cholera is defined by the term $\frac{B}{K+B}$. The model will take an assumption that infected individuals only acquire the bacteria from the environment. The pathogen population grows logistically and the bacteria enter the pathogen reservoir of $Vibrio\ cholerae$ at the rate $CB(1-\frac{B(t)}{K})$, proportional to bacteria density in this class, where $C > 0$ is the per capita growth rate for $Vibrio\ cholerae$. The bacteria shed rate due to rehydration only is d_1 and d_2 is the bacteria shed rate due to both rehydration and administration of antibiotics such that $d_1 = d_2$ and bacteria death rate is given by μ_b.
The total population is given by the equation;

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

The flow chart diagram for the dynamics of the transmission is given by the figure below.

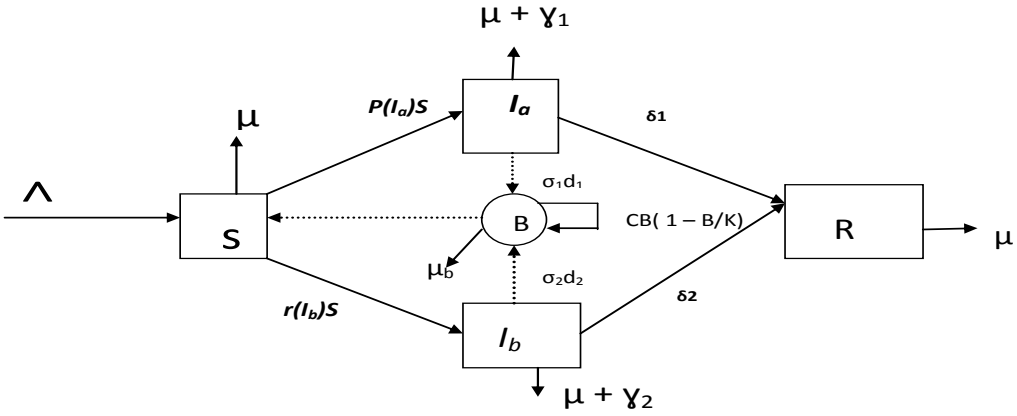

Figure 3.1: The model flow diagram

The system of differential equations describing the model is.

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - p(I_a)S - r(I_b)S - \mu S \\
\frac{dI_a}{dt} &= p(I_a)S - (\mu + \delta_1 + \gamma_1)I_a \\
\frac{dI_b}{dt} &= r(I_b)S - (\mu + \delta_2 + \gamma_2)I_b \\
\frac{dR}{dt} &= \delta_1 I_a + \delta_2 I_b - \mu R \\
\frac{dB}{dt} &= C(1 - \frac{B}{K})B + d_1 I_a \sigma_1 + d_2 I_b \sigma_2 - \mu_b B
\end{aligned} \tag{3.2}$$

where

$$\begin{aligned}
p(I_a) &= [\frac{\alpha B}{K + B}]I_a \\
r(I_b) &= [\frac{\alpha B}{K + B}]I_b.
\end{aligned} \tag{3.3}$$

Substituting (3.3) into (3.2) yield;

$$\frac{dS}{dt} = \Lambda - [\frac{\alpha B}{K + B}]I_a S - [\frac{\alpha B}{K + B}]I_b S - \mu S$$

$$\begin{aligned}
\frac{dI_a}{dt} &= [\frac{\alpha B}{K+B}]I_a S - (\mu + \delta_1 + \gamma_1)I_a \\
\frac{dI_b}{dt} &= [\frac{\alpha B}{K+B}]I_b S - (\mu + \delta_2 + \gamma_2)I_b \\
\frac{dR}{dt} &= \delta_1 I_a + \delta_2 I_b - \mu R \\
\frac{dB}{dt} &= C(1 - \frac{B}{K})B + d_1 I_a \sigma_1 + d_2 I_b \sigma_2 - \mu_b B
\end{aligned} \tag{3.4}$$

Suppose that the initial condition for the system (3.4) takes the form:

$$S(t_0) = S(0), I(t_0) = (I_a, I_b) = I(0) = 0, R(t_0) = R(0), B(t_0) = B(0); t_0 = 0 \tag{3.5}$$

3.3 Positivity and Boundedness of Solutions of the Model

Since in our model we are studying human population, all solutions for the System of Equation (3.4) are all positive for $t \geq 0$.

Proposition 3.3.1. *Solutions of System (3.4) with initial condition (3.5) are bounded for $t \geq 0$ such that $\{S(t) + I_a(t) + I_b(t) + R(t)\} \in \mathbb{R}^4_+$ for $t \geq 0$.*

Proof. From Proposition (3.3.1) the solutions of the system (3.4) given the initial condition (3.5) are positive for all $t \geq 0$

Consider the region $D = \{(S, I_a, I_b, R) \in \mathbb{R}^4_+ : N \leq \frac{\Lambda}{\mu}\}$. Let $N(t) = S(t) + I_a(t) + I_b(t) + R(t)$. From the system of equation (3.4), we have

$$N'(t) = \Lambda - \mu N - (\gamma_1 I_a + \gamma_2 I_b) \leq \Lambda - \mu N(t)$$

$$(Ne^{\mu t})' \leq \Lambda e^{\mu t}$$

$$Ne^{\mu t} \leq \frac{\Lambda}{\mu} e^{\mu t} + C$$

$$\lim_{t \to \infty} N \leq \frac{\Lambda}{\mu} + Ce^{-\mu t}$$

$$N \leq \frac{\Lambda}{\mu}$$

Since solutions of our model are positive and bounded then the model is well-posed.

□

3.4 Basic reproduction number, R_0

Definition 3.4.1. *The basic reproduction number (R_0) is the average number of secondary infections due to a single infectious individual introduced in a fully susceptible population. If $R_0< 1$ it means the disease is eradicated in the population and $R_0>1$ means the disease is persistent in the population*

The constant R_o is determined by the method of next generation matrix approach given by Van *et al*[21]. Consider the matrix

$$M = FV^{-1}.$$

F is the Jacobian of $\mathcal{F}$ which refers to the rate of new infections and V is the Jacobian of $\mathcal{V}$ which refers to the rate of transfer of infectious individuals in and out from one compartment to another. From the system (3.4) the associated matrices are;

$$\mathcal{F} = \begin{pmatrix} \frac{\alpha B}{K+B} SI_a \\ \frac{\alpha B}{K+B} SI_b \\ 0 \\ 0 \end{pmatrix} \tag{3.6}$$

$$\mathcal{V} = \begin{pmatrix} (\mu + \delta_1 + \gamma_1)I_a \\ (\mu + \delta_2 + \gamma_2)I_b \\ -(\delta_1 I_a + \delta_2 I_b) + \mu R \\ (-d_1\sigma_1 I_a - d_2\sigma_2 I_b) + \mu_b B \end{pmatrix} \tag{3.7}$$

The Jacobian matrices of (3.6) and (3.7) evaluated at DFE yield;

$$F = \begin{pmatrix} \frac{\Lambda}{\mu}(\frac{\alpha B}{K+B}) & 0 & 0 & 0 \\ \frac{\Lambda}{\mu}(\frac{\alpha B}{K+B}) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{3.8}$$

$$V = \begin{pmatrix} (\mu + \delta_1 + \gamma_1) & 0 & 0 & 0 \\ 0 & (\mu + \delta_2 + \gamma_2) & 0 & 0 \\ -\delta_1 & -\delta_2 & \mu & 0 \\ -d_1\sigma_1 & -d_2\sigma_2 & 0 & \mu_b \end{pmatrix} \tag{3.9}$$

the inverse of matrix V is;

$$V^{-1} = \begin{pmatrix} (\frac{1}{(\mu+\delta_1+\gamma_1)}) & 0 & 0 & 0 \\ 0 & (\frac{1}{(\mu+\delta_2+\gamma_2)}) & 0 & 0 \\ (\frac{-\delta_1}{(\mu+\delta_1+\gamma_1)\mu}) & (\frac{-\delta_2}{(\mu+\delta_2+\gamma_2)\mu} & \frac{1}{\mu} & 0 \\ (\frac{-d_1\sigma_1}{(\mu+\delta_1+\gamma_1)\mu_b}) & (\frac{-d_2\sigma_2}{(\mu+\delta_2+\gamma_2)\mu_b}) & 0 & \frac{1}{\mu_b} \end{pmatrix} \tag{3.10}$$

$$M = FV^{-1} = \begin{pmatrix} (\frac{\Lambda\alpha B}{\mu(K+B)(\mu+\delta_1+\gamma_1)} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{3.11}$$

The reproduction number $R_0 = \rho(FV^{-1})$, is the spectral radius of the matrix FV^{-1}. Therefore;

$$R_0 = \frac{\Lambda\alpha B}{\mu(K+B)(\mu+\delta_1+\gamma_1)} \tag{3.12}$$

3.5 Disease Free Equilibrium (DFE) point

Disease Free Equilibrium is defined as the state at which no cholera disease is present in the population.

Proposition 3.5.1. *For the model system (3.4) there always exists a DFE point denoted by* $E^0 = (S^0, I_a^0, I_b^0, R^0, B^0) = (\frac{\wedge}{\mu}, 0, 0, 0, 0)$.

Proof. At DFE, $I = 0$,$R = 0$,$B = 0$ Therefore considering the first equation in system (3.4) and replacing $I_a = I_b = 0$ yields;

$$\Lambda - \mu S = 0$$

Making S the subject yield;

$$S = \frac{\Lambda}{\mu} \tag{3.13}$$

Therefore the DFE $E^0(S^0, I_a^0, I_b^0, R^0, B^0) = (\frac{\wedge}{\mu}, 0, 0, 0, 0)$ □

3.6 Stability Analysis of the equilibrium points

3.6.1 Local Stability of the Disease Free Equilibrium (DFE)

The stability of equilibrium point is related to the basic reproduction number R_0 of the model.

Proposition 3.6.1. *For any time* $t \geq 0$, *the disease free equilibrium* $E^0 = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$ *of system (3.4) is locally asymptotically stable when* $R_0 < 1$ *and unstable when* $R_0 > 1$.

Proof. The jacobian matrix of (3.4) is given by;

$$J = \begin{pmatrix} -(\frac{\alpha B}{K+B})I_a - (\frac{\alpha B}{K+B})I_b - \mu & -(\frac{\alpha B}{K+B})S & -(\frac{\alpha B}{K+B})S & 0 & 0 \\ (\frac{\alpha B}{K+B})I_a & (\frac{\alpha B}{K+B})S - (\mu+\delta_1+\gamma_1) & 0 & 0 & 0 \\ (\frac{\alpha B}{K+B})I_b & 0 & (\frac{\alpha B}{K+B})S - (\mu+\delta_2+\gamma_2) & 0 & 0 \\ 0 & \delta_1 & \delta_2 & -\mu & 0 \\ 0 & d_1\sigma_1 & d_2\sigma_2 & 0 & \theta \end{pmatrix} \tag{3.14}$$

where

$$\theta = C(1 - \frac{2B}{K}) - \mu_b$$

Substituting the DFE points $E^0(S^0, I_a^0, I_b^0, R^0, B^0) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$ into (3.14) yield;

$$J_{DFE} = \begin{pmatrix} -\mu & \frac{-\Lambda}{\mu}(\frac{\alpha B}{K+B}) & \frac{-\Lambda}{\mu}(\frac{\alpha B}{K+B}) & 0 & 0 \\ 0 & \frac{\Lambda}{\mu}(\frac{\alpha B}{K+B}) - (\mu+\delta_1+\gamma_1) & 0 & 0 & 0 \\ 0 & 0 & \frac{\Lambda}{\mu}(\frac{\alpha B}{K+B}) - (\mu+\delta_2+\gamma_2) & 0 & 0 \\ 0 & \delta_1 & \delta_2 & -\mu & 0 \\ 0 & d_1\sigma_1 & d_2\sigma_2 & 0 & \theta \end{pmatrix} \tag{3.15}$$

The DFE in terms of R_0 yield;

$$J_{DFE} = \begin{pmatrix} -\mu & -R_0(\mu+\delta_1+\gamma_1) & -R_0(\mu+\delta_1+\gamma_1) & 0 & 0 \\ 0 & (\mu+\delta_1+\gamma_1)(R_0-1) & 0 & 0 & 0 \\ 0 & 0 & (R_0-1)\mu + R_0(\delta_1+\gamma_1) - (\delta_2+\gamma_2) & 0 & 0 \\ 0 & \delta_1 & \delta_2 & -\mu & 0 \\ 0 & d_1\sigma_1 & d_2\sigma_2 & 0 & C-\mu_b \end{pmatrix} \tag{3.16}$$

The matrix has eigenvalues; $\lambda = -\mu, (\mu+\delta_1+\gamma_1)(R_0-1), (R_0-1)\mu + R_0(\delta_1 + \gamma_1) - (\delta_2+\gamma_2), -\mu, C-\mu_b$. For local asymptotic stability, all real parts of λ should be negative. The eigenvalues $\lambda = -\mu, C-\mu_b$ have negative real parts, also the eigenvalues λ=$\{(\mu+\delta_1+\gamma_1)(R_0-1), (R_0-1)\mu + R_0(\delta_1+\gamma_1) - (\delta_2+\gamma_2)\}$ are negative if and only if $R_0 < 1$. Hence the DFE is locally asymptotically stable.

□

3.6.2 Global Stability of the Disease Free Equilibrium (DFE)

In this section, the global asymptotic stability of the DFE of the model system (3.4) is explored.

Theorem 3.6.1. *The DFE of the system (3.4) is globally asymptotically stable whenever the* $R_0 < 1$ *and unstable if* $R_0 > 1$.

Proof. It follows that $S = N' - I_a - I_b - R$ at the steady state. The proof is based on Comparison Theorem Lakshmikanthan *et al*[14] to prove the global stability. Hence, we have;

$$\begin{pmatrix} I_a' \\ I_b' \end{pmatrix} = (F - V) - \mathcal{F} \begin{pmatrix} I_a \\ I_b \end{pmatrix}$$

such that $\{I_a(t), I_b(t)\} \rightarrow (0, 0)$ as $t \rightarrow \infty$ hence;

$$\begin{pmatrix} I_a' \\ I_b' \end{pmatrix} = (F - V)$$

where;

$$F - V = \begin{pmatrix} (\mu + \delta_1 + \gamma_1)(R_0 - 1) & 0 & 0 & 0 \\ (\mu + \delta_1 + \gamma_1)R_0 & -(\mu + \delta_2 + \gamma_2) & 0 & 0 \\ \delta_1 & \delta_2 & -\mu & 0 \\ d_1\sigma_1 & d_1\sigma_2 & 0 & -\mu_b \end{pmatrix} \tag{3.17}$$

Thus all the eigenvalues of the lower triangular matrix $(F - V)$ have negative real parts as seen in matrix (3.17). It follows that the Jacobian matrix of system (3.4) is stable whenever $R_0 < 1$. Consequently substituting $I_a = I_b = R = B = 0$ into system (3.4), $S(t) \rightarrow S(0)$ as $t \rightarrow \infty$. We therefore conclude that $I_a = I_b = R = B = 0$ as $t \rightarrow \infty$. It follows that the DFE is globally asymptotically stable whenever $R_0 < 1$. □

3.6.3 Local Stability of the Endemic Equilibrium (EE) points

Theorem 3.6.2. *The endemic equilibrium* $E^*(S^*, I_a^*, I_b^*, R^*)$ *of system (3.4) is locally asymptotically stable whenever* $R_0 > 1$.

Proof. Using the system (3.4) and equating the right hand side of 3.4 to 0 and solving the system of equation simultaneously using MATLAB software to find the endemic equilibrium states, the endemic equilibrium points are determined under two cases;

CASE I: When $I_b^* = 0$ we have;

$$S^* = \frac{K+B}{\alpha B}(\mu + \delta_1 + \gamma_1)$$

$$R^* = \frac{\delta_1[\Lambda(\frac{\alpha B}{K+B}) - \mu(\mu + \delta_1 + \gamma_1)]}{(\frac{\alpha B}{K+B})[\mu(\mu + \delta_1 + \gamma_1) - \alpha\delta_1]}$$

$$I_a^* = \frac{\mu[-\Lambda(\frac{\alpha B}{K+B}) - \mu(\mu + \delta_1 + \gamma_1)]}{(\frac{\alpha B}{K+B})[\mu(\mu + \delta_1 + \gamma_1) - \alpha\delta_1]}$$

$$B^* = \frac{K(C-\mu_b) \pm \sqrt{K^2(C-\mu_b)^2 - 4CKd_1 I_a^* \sigma_1}}{2C}$$

Writing I_a^* in terms of R_0 yield;

$$I_a^* = \frac{\mu[(-\mu R_0(\mu + \delta_1 + \gamma_1) - \mu(\mu + \delta_1 + \gamma_1)]}{(\mu + \delta_1 + \gamma_1)(\frac{\mu R_0}{\Lambda})[\mu(\mu + \delta_1 + \gamma_1) - \delta_1]}$$

The system (3.4) is also solved simultaneously under the second case using MATLAB software and yields;

CASE II: When $I_a^* = 0$ we have;

$$S^* = \frac{K+B}{\alpha B}(\mu + \delta_2 + \gamma_2)$$

$$R^* = \frac{\delta_2[-\Lambda(\frac{\alpha B}{K+B}) + \mu(\mu + \delta_2 + \gamma_2)]}{(\frac{\alpha B}{K+B})[\alpha\delta_2 - \mu(\mu + \delta_2 + \gamma_2)]}$$

$$I_b^* = \frac{\mu[-\Lambda(\frac{\alpha B}{K+B}) + \mu(\mu + \delta_2 + \gamma_2)]}{(\frac{\alpha B}{K+B})[\delta_2 - \mu(\mu + \delta_2 + \gamma_2)]}$$

$$B^* = \frac{K(C-\mu_b) \pm \sqrt{K^2(C-\mu_b)^2 - 4CKd_2 I_b^* \sigma_2}}{2C}$$

Writing I_b^* in terms of R_0 yield;

$$I_b^* = \frac{\mu[(-\mu R_0(\mu + \delta_1 + \gamma_1) + \mu(\mu + \delta_2 + \gamma_2)]}{(\mu + \delta_1 + \gamma_1)(\frac{\mu R_0}{\Lambda})[\delta_2 - \mu(\mu + \delta_2 + \gamma_2)]}$$

Substituting the endemic states in the linearized matrix of system (3.4) when $I_a^* = 0$ yield;

$$J_{EE} = \begin{pmatrix} (-\frac{\alpha B}{K+B})I_b^* - \mu & (-\frac{\alpha B}{K+B})S^* & (-\frac{\alpha B}{K+B})S^* & 0 \\ 0 & (\frac{\alpha B}{K+B})S^* - (\mu+\delta_1+\gamma_1) & 0 & 0 \\ (\frac{\alpha B}{K+B})I_b^* & 0 & (\frac{\alpha B}{K+B})S^* - (\mu+\delta_2+\gamma_2) & 0 \\ 0 & \delta_1 & \delta_2 & -\mu \end{pmatrix} \tag{3.18}$$

Substituting the endemic states in matrix (3.18) and determining the eigenvalues when $I_a^* = 0$ yield; $\lambda_1 = -\mu$, $\lambda_2 = (\mu+\delta_2+\gamma_2) - (\mu+\delta_1+\gamma_1)$ and $\lambda_{3,4}$ $= \frac{1}{2}[-(\frac{\mu(-\mu R_0)(\mu+\delta_1+\gamma_1)+\mu(\mu+\delta_2+\gamma_2)}{\delta_2-\mu(\mu+\delta_2+\gamma_2)})]$
$\pm \frac{1}{2}\sqrt{[(\frac{\mu(-\mu R_0)(\mu+\delta_1+\gamma_1)+\mu(\mu+\delta_2+\gamma_2)}{\delta_2-\mu(\mu+\delta_2+\gamma_2)})^2 - 4(\mu+\delta_2+\gamma_2)(\frac{\mu(\mu R_0)(\mu+\delta_1+\gamma_1)+\mu(\mu+\delta_2+\gamma_2)}{\delta_2-\mu(\mu+\delta_2+\gamma_2)})]}$
The endemic equilibrium (EE) of system (3.4) locally asymptotically stable for $\lambda_1 = -\mu$ and for $\lambda_2 = (\mu+\delta_2+\gamma_2)-(\mu+\delta_1+\gamma_1)$ if and only if $(\mu+\delta_1+\gamma_1) > (\mu+\delta_2+\gamma_2)$. From $\lambda_{3,4}$ we have;

$$(\frac{\mu[(\mu R_0)(\mu+\delta_1+\gamma_1) - \mu(\mu+\delta_2+\gamma_2)]}{\mu(\mu+\delta_2+\gamma_2) - \delta_2}) > 0$$

$$\frac{\mu^2}{\mu - \frac{\delta_2}{(\mu+\delta_2+\gamma_2)}}\{\frac{R_0(\mu+\delta_1+\gamma_1)}{(\mu+\delta_2+\gamma_2)} - 1\} > 0$$

$$\{\frac{R_0(\mu+\delta_1+\gamma_1)}{(\mu+\delta_2+\gamma_2)} - 1\} > 0$$

We have

$$R_0 > \{\frac{(\mu+\delta_1+\gamma_1)}{(\mu+\delta_2+\gamma_2)}\}$$

From

$$(\mu+\delta_1+\gamma_1) > (\mu+\delta_2+\gamma_2)$$

It implies that

$$(\mu+\delta_1+\gamma_1) > (\mu+\delta_2+\gamma_2) \approx 1$$

As a result $R_0 > 1$. Therefore for $R_0 > 1$, EE is locally asymptotically stable.

□

Theorem 3.6.3. *For the system (3.4), endemic equilibrium is locally asymptotically stable if and only if $R_0 > 1$ for $I_b^* = 0$.*

Proof. Substituting the endemic states in the linearized Jacobian matrix of system (3.4) when $I_b^* = 0$ yields,

$$J_{EE} = \begin{pmatrix} (-\frac{\alpha B}{K+B})I_a^* - \mu & (-\frac{\alpha B}{K+B})S^* & (-\frac{\alpha B}{K+B})S^* & 0 \\ (\frac{\alpha B}{K+B})I_a^* & (\frac{\alpha B}{K+B})S^* - (\mu+\delta_1+\gamma_1) & 0 & 0 \\ 0 & 0 & (\frac{\alpha B}{K+B})S^* - (\mu+\delta_2+\gamma_2) & 0 \\ 0 & \delta_1 & \delta_2 & -\mu \end{pmatrix} \tag{3.19}$$

Substituting the endemic states in matrix (3.19) and determining the eigenvalues when $I_b^* = 0$ yield; $\lambda_1 = -\mu$, $\lambda_2 = (\mu+\delta_1+\gamma_1)-(\mu+\delta_2+\gamma_2)$ and $\lambda_{3,4} = \frac{1}{2}[-(\frac{\mu(-\mu R_0)(\mu+\delta_1+\gamma_1)+\mu(\mu+\delta_1+\gamma}{\mu(\mu+\delta_1+\gamma_1)-\delta_1}$ $\pm\frac{1}{2}\sqrt{[(\frac{\mu(-\mu R_0)(\mu+\delta_1+\gamma_1)+\mu(\mu+\delta_1+\gamma_1)}{\mu(\mu+\delta_1+\gamma_1)-\delta_1)}) - \mu)^2 - 4((\mu+\delta_2+\gamma_2))(\frac{\mu(\mu R_0)(\mu+\delta_1+\gamma_1)+\mu(\mu+\delta_1+\gamma_1)}{\mu(\mu+\delta_1+\gamma_1)-\delta_1}))]}$

Therefore endemic equilibrium (EE) is locally asymptotically stable for $\lambda_1 = -\mu$ and for $\lambda_2 = (\mu+\delta_1+\gamma_1) - (\mu+\delta_2+\gamma_2)$ if and only if $(\mu+\delta_2+\gamma_2) > (\mu+\delta_1+\gamma_1)$. From $\lambda_{3,4}$ we have;

$$\begin{gathered} (\frac{\mu[(\mu R_0)(\mu+\delta_1+\gamma_1) - \mu(\mu+\delta_1+\gamma_1)]}{\delta_1 - \mu(\mu+\delta_1+\gamma_1))}) > 0 \\ (\frac{\mu^2(\mu+\delta_1+\gamma_1)[R_0-1]}{\delta_1 - \mu(\mu+\delta_1+\gamma_1))}) > 0 \\ \frac{\mu^2}{\frac{\delta_1}{(\mu+\delta_1+\gamma_1)} - \mu}[R_0 - 1] > 0 \\ [R_0 - 1] > 0 \end{gathered}$$

It implies that $R_0 > 1$. For $R_0 > 1$, EE is locally asymptotically stable. This ends the proof. □

3.7 Numerical Simulation

Introduction

In this section, we use MATLAB software to generate the numerical simulations describing the theoretical results for the system (3.4). The numerical results depend on the particular units chosen. The parameter values used in the simulation are either obtained from literature or estimated. The parameter values have been varied to better understand how rehydration and antibiotics use reduce cholera mortality.

3.7.1 Parameter Values

The parameters values below are described in Table (3.2).

Table 3.2: Parameter values for the Cholera Model

Parameters	Range/Value	Source
Λ	10^4	Estimated
K	10^6 $cells\ ml^{-1}$	[2]
α	0.05	Varies
μ	0.0068	[5]
δ_1	0.2 day^{-1}	[16]
δ_2	0.25 day^{-1}	Estimated
γ_1	0.015 day^{-1}	[11]
γ_2	0.025 day^{-1}	Estimated
σ_1	0.6	[16]
σ_2	0.75	Estimated
μ_b	0.33 day^{-1}	[4]
C	0.73 day^{-1}	[16]
d_1	10 $cells\ per\ ml\ day^{-1}$	[23]
d_2	10 $cells\ per\ ml\ day^{-1}$	Estimated

3.7.2 Simulation Results

Graph of bacteria population versus time

Figure 3.2 below shows the bacteria population growth curve in absence of disease. The graph shows that in the absence of the disease at $t \geq 0$, the bacteria population grows logistically to the carrying capacity when the disease free equilibrium is globally asymptotically stable as shown in theorem (3.6.1). This implies that no rehydration and antibiotic is given to individuals since there is no infection, as a result there is no influence to the stability of the disease free equilibrium.

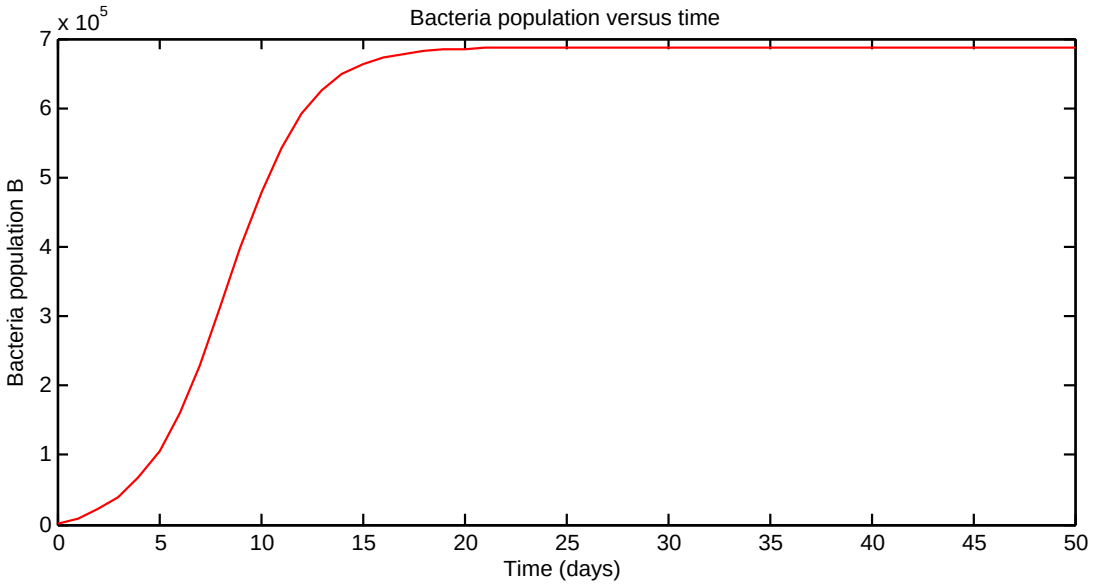

Figure 3.2: bacteria population growth curve versus time

Graph of individuals with bacteria in the intestine against time with rehydration

Figure 3.3 below shows the infection curve for cholera model with rehydration of individuals infected with the bacteria in the intestine only. Initially, there is a sharp increase in the number of those infected with the bacteria in the intestine only. This means that even though they have been rehydrated, they are not cured immediately. From the graph it can be seen that after the first day,the infection level starts reducing with an increase in rehydration hence there is recovery.

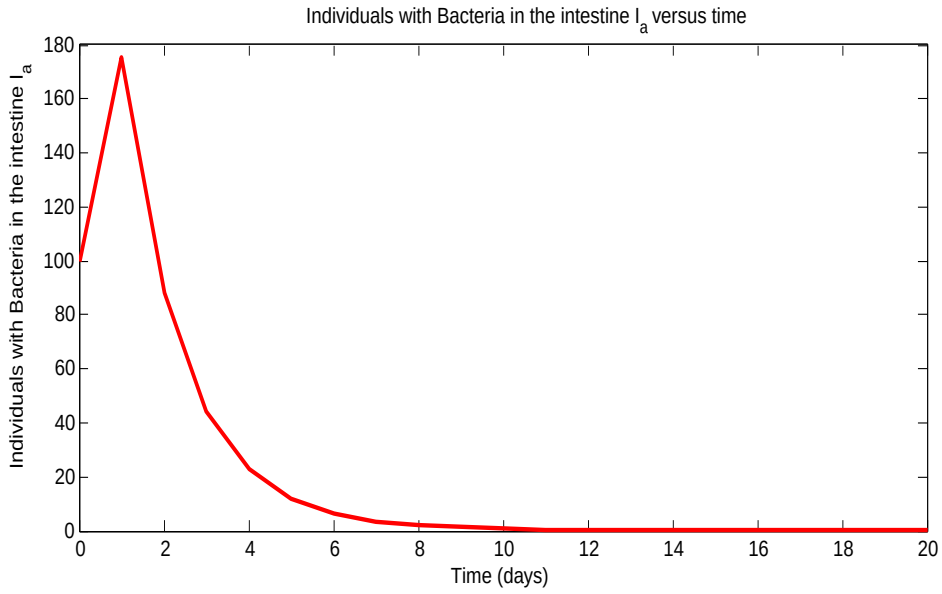

Figure 3.3: A graph showing how the number of individuals infected with bacteria in the intestine only varies with time in days after rehydration

Graph of individuals with bacteria in both the intestine and the bloodstream against time with rehydration and antibiotic administration

Figure 3.4 below shows the infection curve for cholera model of individuals infected with the bacteria in both the intestine and the bloodstream. Initially, there is a sharp increase in the number of those infected. This shows that even though they have been rehydrated and antibiotics given , they do not start recovering immediately. Though the curve clearly shows that they start recovering after the first day of treatment. As expected that the level is supposed to be slightly lower when both rehydration and antibiotic is given, that is not the case. This could be due to large presence of bacteria to the infected individuals at this level. The curve also shows that the disease still remains endemic.

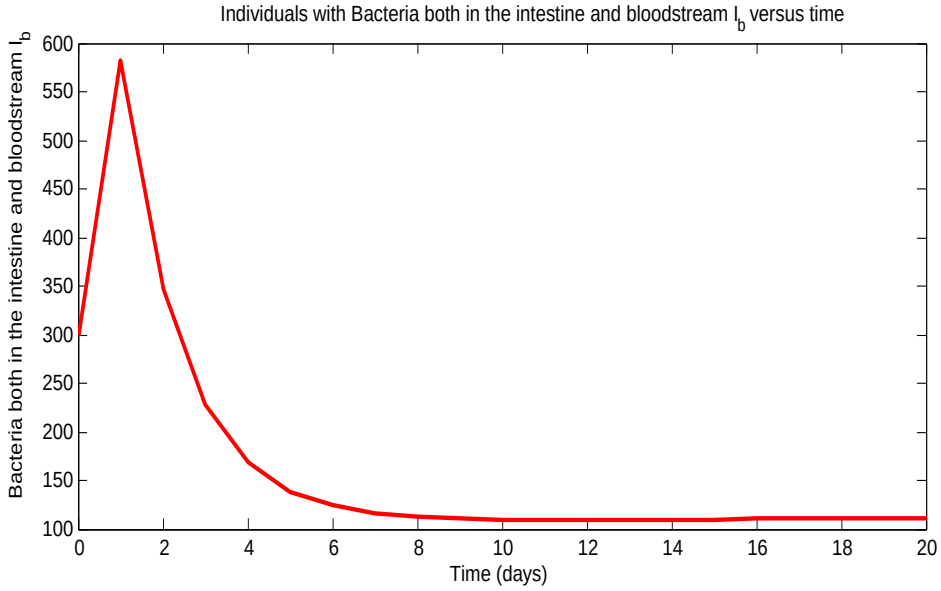

Figure 3.4: A graph showing how the number of individuals infected with bacteria in both the intestine and bloodstream varies with time in days after rehydration and antibiotic administration

Graph of I_a, I_b and R against time

Figure 3.5 below shows that rehydrating those infected with the bacteria in the intestine only (I_a) and rehydrating and administering antibiotics to those infected with the bacteria in both the intestine and the bloodstream (I_b) reduces cholera deaths hence they recover and the curve shows an increase in number of recovered individuals as time increases since they acquire temporal immunity.

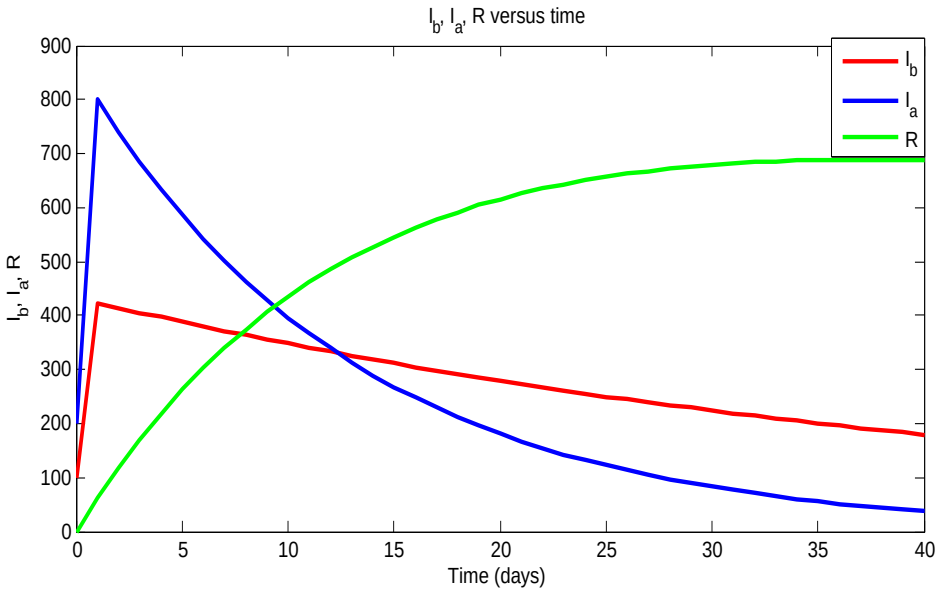

Figure 3.5: a graph showing the relationship between I_a, I_b and R against time in days

CHAPTER 4

CONCLUSIONS AND RECOMMENDATIONS

4.0.1 Introduction

This research was focused on the role of rehydration and antibiotic treatment in reduction of cholera mortality. In this chapter we therefore make conclusions in relation to the objectives of the study and give recommendations.

4.0.2 Conclusion

We have presented a cholera epidemiological model assessing the role of rehydration and antibiotic treatment in reduction of cholera mortality. There is only environmental to human transmission pathway. The basic reproduction number R_0 plays a crucial role in determining the epidemic and endemic dynamics. We have shown that the DFE is locally asymptotically stable when $R_0 < 1$, and unstable when $R_0 > 1$. The DFE have also been shown to be globally stable when $R_0 < 1$. This means that given any perturbation, the disease free equilibrium remains stable.

The endemic equilibrium (EE) has also been shown to be locally asymptotically stable when $R_0 > 1$.

Simulation results show that rehydration plays a major role in reducing cholera deaths when the bacteria is in the intestine only, when rehydration is done and antibiotics given to individuals infected with the bacteria in both the intestine and the bloodstream, cholera deaths are reduced though it still remains endemic with both rehydration and antibiotic administration.

4.0.3 Recommendation

Any decision taken to reduce cholera death should be done in good time. Once individuals have been discovered to have been infected with the bacteria they should be immediately rehydrated and later antibiotics given so as to kill all the microbes.

We finally recommend to health practitioners to equip the hospital laboratories with equipments for testing of cholera, sufficient Ringer-Lactate solutions for rehydration and sufficient antibiotics for timely treatment of cholera cases.

4.0.4 Future work

In future, there will be need to model "The Impact of delay in Rehydration and Antibiotic treatment among cholera patients in a population that grows logistically."

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