Journal of Progressive Research in Mathematics
Vol 19,2 - 2022 — E-ISSN: 2395-0218
http://www.scitecresearch.com/journals/index.php/jprm

Mathematical Modelling of Cholera Incorporating the Dynamics of the Induced Achlorhydria Condition and Treatment

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Received: October 03, 2022; Accepted: October 13, 2022; Published: November 02, 2022

Abstract

Cholera is an infectious disease caused by the bacterium *Vibrio cholerae* rampant in countries with inadequate access to clean water and proper sanitation. In this work a mathematical model for cholera incorporating the dynamics of the induced achlorhydria condition and treatment is analysed. Michaelis-menten equation in microbiology is used to show variation in pH level of the hydrochloric acid in the digestive system. *Vibrio cholerae* are acid labile and thrive well in alkaline medium. Once the gastric pH is raised by factors like antacid drugs or surgery the stomach medium become suitable for *Vibrio cholerae* to thrive and multiply very fast than healthy people. This lead to cholera transmission as the infected individuals with induced achlorhydria condition shed more folds of *Vibrio cholerae* to the environment. If individuals with achlorhydria condition are treated, the effect of cholera outbreak is reduced. The existence and stability of the equilibrium points is established. Analysis of the model show that the disease free equilibrium is both locally and globally asymptotically stable when the basic reproduction number is less than unity, while the endemic equilibrium is locally asymptotically stable when the reproduction number is greater than unity. Numerical simulations is done using MATLAB software to show the effect of the induced achlorhydria condition on the spread of cholera and individuals with this condition suffer severe infection during cholera outbreak.

Keywords

Cholera, Mathematical model, Induced achlorhydria condition, Michaelis-menten equation, Stability analysis

How to cite this paper: Ngari, C., Ngari, C. G., Okongo, M., Ochwach, J. (2022) Mathematical Modelling of Cholera Incorporating the Dynamics of the Induced Achlorhydria Condition and Treatment. Journal of Progressive Research in Mathematics, 19(2), 60-88. Retrieved from http://scitecresearch.com/journals/index.php/jprm/article/view/2168

1. Introduction

Modelling is a technique for simulating real-life situations with mathematical equations in order to predict future behavior by generating a simplified representation of a real system [1]. Modeling of infectious diseases is a tool that have been used to study the mechanisms by which diseases spread, predict the future course of an outbreak and evaluate strategies to control an epidemic [2]. Studies of the emergence of infectious diseases are likely to become increasingly important with increase in human and livestock population and increasing stress placed on aquatic reservoirs [3].

Cholera is a public health issue most of the time occurring in the African continent [4]. Access to clean water through improved water network systems and sanitary facilities therefore remains the most effective means of preventing cholera outbreaks [5]. Studies of gastric acidity and cholera are of interest, *Vibrio cholerae* is a very acid-labile organism and it has been proposed that normal gastric acidity presents a barrier to the establishment of intestinal infection [6]. Several models have been formulated and analysed to explain the dynamics of cholera transmission. [7] Studied cholera dynamics with prevention and control, therapeutic treatment was in form of administration of antibiotics or re-hydration salts, vaccination and therapeutic treatment were incorporated as prevention and control strategies against cholera transmission, according to this study availability and potency of these interventions were capable of averting 120 000 deaths due to cholera.

[8] Developed a model on mathematical assessment of the role of environmental factors on the dynamical transmission of cholera, the objective was to investigate the impact of environmental factors on the dynamical transmission of cholera within a human population on the persistence of the disease. [9] Discussed a model on cholera with hyper infectious and hypo infectious *vibrios*, in which both humans and environment to humans transmissions were considered. A combination with quarantine, sanitation, vaccination and treatment strategy is more efficient to prevent, control and eradicate cholera. [10] Developed a model considering optimal control of cholera on presence of asymptotic transmission and control interventions (social mobilization, drug/oral re-hydration solution and safe water), the goal was to develop (deterministic and stochastic) mathematical models of cholera transmission and control dynamics with the aim of investigating the effect of the three control interventions against cholera transmission in order to find optimal control strategies. It was advised that the use of multiple control interventions be adopted for cholera in areas where there were sufficient resources. However, in areas where there are limited or lack of resources, it was advised that treatment of the asymptomatic individuals with drug or administration of oral re-hydration solution to the infected should be used.

Achlorhydria refer to condition in which production of hydrochloric acid in the digestive system is respectively absent or reduced, it is usually secondary to an underlying medical condition. Stomach pH in fasting, healthy people is between pH 2.5 and serves as a barrier to food-borne pathogens[11]. *Vibrio cholerae* survived well in normal gastric juice when the pH was adjusted to neutrality but were rapidly killed at pH values less than 4.8 [6]. There is evidence that patients with hypochlorhydria or achlorhydria or who have been treated with proton pump inhibitors or H-2 receptor antagonists are more susceptible to *Vibrio cholerae* than healthy persons [12]. Proton pump inhibitors are available increasingly without prescription, so that people can self-medicate without realizing that this might mean an increased risk of cholera disease. In a study conducted in the USA, adult volunteers experimentally challenged with virulent strains of *Vibrio cholerae* only developed cholera after the gastric pH in the volunteers was raised by antacid drugs [13]. In this paper, we seek to understand the effects of the induced achlorhydria condition on the transmission of cholera.

2. Model Formulation

The model is adopted from the classical SIR model. The model describe the transmission of cholera incorporating the dynamic of the induced achlorhydria condition and treatment. The total population is denoted as N which subdivide into the following classes, (S) as the susceptible individuals, (I_c) the cholera infected individuals, (I_{cr}) the cholera infected individual with induced achlorhydria condition, (T_c) those seeking treatment for cholera and (R) individual who have recovered from cholera (S, I_c, I_{cr}, T_c, R). The main feature of the model is that the force of

infection, λ is obtained by mass-mixing of individuals in a population, β infection rate is also considered. Infected individuals who joined the class I_c can progress into I_{cr} due to implications of the induced achlorhydria condition or may die out naturally. After progressing into this group and treatment of achlorhydria is done or correct mechanism by enhancing production of hydrochloric acid is done individual progress to (T_c) where they seek treatment for cholera at a rate α. Individuals recover from cholera and join class (R) and return to susceptible class (S) after gaining temporal immunity against cholera. The next-generation matrix is used to derive the basic reproduction number, for a compartmental model of the spread of infectious diseases in population dynamics, it is used to compute the basic reproduction number for structured population models.

2.1. Model Assumptions

i. We assume the people under treatment have lower infectivity and death rate as it's believed treatment significantly lower transmission and death rate of cholera.
ii. All people have equal chance of contracting cholera.
iii. Uniform mass mixing of population is considered.
iv. The population is considered to be homogeneous.
v. Individuals infected with cholera and have induced achlorhydria condition contribute more to the force of infection than those individuals infected with cholera alone and those at treatment class.

Table 1. *Model Variables*

Variables	Description
S(t)	The number of susceptible individuals in a population at time t
$I_c(t)$	The number of cholera infective in a population at time t
$I_{cr}(t)$	Individuals infected with cholera and have induced Achlorhydria condition at time t
$T_c(t)$	The number of cholera patient seeking treatment at time t
R(t)	The number of recovered individuals at time t

Table 2. *Model parameters*

Variables	Description
π	Rate of recruitment into the susceptible class (S)
μ	Net natural death rate of the individuals
λ	Transmission rate/force of infection
α	Rate of seeking treatment for the infected class
δ_2	Death rate due to cholera infection for the treatment class
θ_1	Death rate due to achlorhydria condition
ω	Rate of recovery for the treatment class
ϕ	Rate of disease recovery rate
A_L	Low pH concentration
A_H	High/normal pH concentration
V_{max}	Maximum acid concentrations
K_M	Acid Constant
β	Infection rate
N	Total population

2.2. Model Equation

$$\frac{dS}{dt} = \pi + \phi R - \mu S - \lambda S \tag{1}$$

$$\frac{dI_c}{dt} = \lambda S - \mu I_c - \alpha I_c - \delta_1 I_c - V_{max}\frac{A_L}{K_M + A_L} I_c \tag{2}$$

$$\frac{dI_{cr}}{dt} = V_{max}\frac{A_L}{K_M + A_L} I_c - \mu I_{cr} - \theta\delta_1 I_{cr} - V_{max}\frac{A_H}{K_M + A_H} I_{cr} \tag{3}$$

$$\frac{dT_c}{dt} = V_{max}\frac{A_H}{K_M + A_H} I_{cr} + \alpha I_c - \delta_2 T_c - \mu T_c - \omega T_c \tag{4}$$

$$\frac{dR}{dt} = \omega T_c - \mu R - \phi R \tag{5}$$

2.3. Positivity of solutions

Theorem 1:
We prove that all solutions of the system of equations (1-5) with positive initial data remained positive for time $t > 0$.

Proof:

We take the system of differential equations (1-5) and it follows directly from the first equation that;

$$\frac{dS}{dt} = \pi + \phi R - \mu S - \lambda S$$

Considering the negative term only we have;

$$\frac{dS}{dt} = -(\mu + \lambda)S$$

By separation of variables and integration, we have;

$$\begin{aligned} \int \frac{dS}{S} &= \int -(\mu + \lambda)dt \\ lnS(t) &= \int_0^t -(\mu + \lambda)ds \\ S &\geq e^{\int_0^t -(\mu+\lambda)+C} \\ S(t) \geq S(0) &\int_0^t -(\mu + \lambda(s))dt > 0. \end{aligned}$$

clearly;

$$S(0)e^{\int_0^t -(\mu+\lambda(s)ds} > 0$$

is non-negative function of t, thus S(t) stays positive. Similarly, by integration and applying the initial conditions, the positivity of I_c (t), I_{cr} (t), T_c(t) and R (t) are proved along the same lines as S (t) accordingly, from the system of equations (1-5), it can be shown that,

$$\begin{aligned} I_c(t) &\geq I_c(0)e^{-[\mu+\alpha+\delta_1+V_{max}\frac{A_L}{K_m+A_L}]}I_c > 0 \\ I_{cr}(t) &\geq I_{cr}(0)e^{-[\mu+\theta\delta_1+V_{max}\frac{A_H}{K_m+A_H}]} > 0 \\ T_c(t) &\geq T_c(0)e^{-[\delta_2+\mu+\omega]T_c} > 0 \\ R(t) &\geq R(0)e^{-[\mu+\phi]R} > 0 \end{aligned}$$

This holds the claim of the theorem for positivity of solutions for the system of equations (1-5). Therefore, S (t), $I_c(t)$, I_{cr} (t), T_c (t) and R (t) stays positive for all future time.

2.4. Boundedness of the system

Let the feasible region be defined by;
$\Omega = S(t), I_c(t), I_{cr}(t), T_c(t)$ and $R(t)$, with the initial conditions $S(0) \geq 0$, $I_c(0) \geq 0$, $I_{cr}(0) \geq 0$, $T_c(0) \geq 0$ and $R(0) \geq 0$. The region Ω is positively invariant and attracting with respect to the system of equations (1-5) for all $t > 0$.

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI_c}{dt} + \frac{dI_{cr}}{dt} + \frac{dT_c}{dt} + \frac{dR}{dt}.$$

In the absence of infection, there are no recovery. Then, initially N (0) = S (0)

$$\frac{dN}{dt} = \pi - \mu S$$

solving the differential equation, by separation of variables

$$\frac{dN}{\pi - \mu S} = dt$$

integrating the differential equation

$$\begin{aligned} \int \frac{dN}{\pi - \mu S} &\leq \int dt \\ \frac{-1}{\mu} ln|\pi - \mu S| &\leq t + A \\ ln|\pi - \mu S| &\geq -\mu(t + A) \\ \pi - \mu S &\geq e^{-\mu t} e^{-\mu A} \end{aligned}$$

where,

$e^{-\mu A} = C$
$\pi - \mu S \geq Ce^{-\mu t}$. At N(0)= N_0 i.e t = 0, N = N_0
$\pi - \mu N_0 = C$.
By rearranging and simplifying

$$\frac{\pi}{\mu} - N \geq \frac{\pi - \mu N_0}{\mu} e^{-\mu t}$$

As $t \to \infty$, the population size $N \to \frac{\pi}{\mu}$ and this implies that;
$0 \leq N < \frac{\pi}{\mu}$ and $N \leq \frac{\pi}{\mu}$, therefore $\Omega = \{S(t), I_c(t), I_{cr}(t), T_c(t), R(t) \in R_+^5; N \leq \frac{\pi}{\mu}\}$. This proves the boundedness of the solutions inside Ω, it implies that all solutions of our system (1-5), starting in Ω and will remains in Ω for all $t > 0$. Thus it is sufficient to consider the dynamics of our system in Ω.

2.5. Disease free equilibrium point (DFE)

The disease free equilibrium point (DFE) of the system (1-5) is obtained by setting all the infectious classes, recovered class and treatment class to zero.

We obtain;

$$\begin{aligned} \frac{dS}{dt} &= \pi + \phi R - \mu S - \lambda S \\ 0 &= \pi + \phi R - \mu S - \lambda S \\ S^0 &= \frac{\pi}{\mu} \end{aligned}$$

The DFE point for the system is given by,
$E^0 = (S^0, I_c^0, I_{cr}^0, T_c^0, R^0) = (\frac{\pi}{\mu}, 0, 0, 0, 0)$.
The DFE point (E^0) is the infection free equilibrium point of the system (1-5), which is numerically illustrated in figure 1.

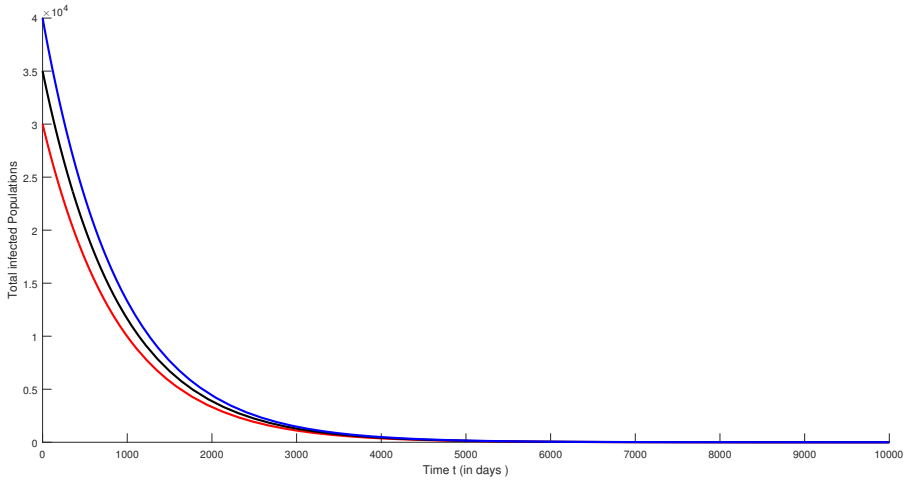

Figure 1. *Total cholera infected individuals with time.(DFE).*

2.6. Computation of basic reproduction number

Using the notation f for a matrix of new infection terms and v for the matrix of the remaining transfer of infection terms. In this system, we got,

f= $\begin{pmatrix} \lambda S \\ 0 \\ 0 \end{pmatrix}$

v= $\begin{pmatrix} (+\mu + \delta_1 + \alpha + V_{max}\frac{A_L}{K_M+A_L})I_c \\ -V_{max}\frac{A_L}{K_M+A_L}I_c + (\mu + \theta\delta_1 + V_{max}\frac{A_H}{K_M+A_H})I_{cr} \\ -V_{max}\frac{A_H}{K_M+A_H}I_{cr} - \alpha I_c + (\delta_2 + \mu + \omega)T_c \end{pmatrix}$

We obtain the matrices F and V by finding the Jacobian matrices of f and v evaluated at DFE respectively to obtain,

F= $\begin{pmatrix} \frac{\beta S^0}{N} & \frac{\beta\ n_1 S^0}{N} & \frac{\beta n_2 S^0}{N} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$

Let Q= $v_{max}\frac{A_L}{K_M+A_L}$, R= $V_{max}\frac{A_H}{K_M+A_H}$ and L=$\delta_2 + \mu + \omega$

$$\text{V=}\begin{pmatrix} (+\mu+\delta_1+\alpha+Q) & 0 & 0 \\ -Q & +(\mu+\theta\delta_1+R) & 0 \\ -\alpha & -R & L \end{pmatrix}$$

$$FV^{-1} = \frac{\beta}{N(Q+\alpha+\mu+\delta_1)} + \frac{Q\beta\eta_1}{N(Q+\alpha+\mu+\delta_1)(R+\mu+\theta\delta_1)} + \frac{\beta\eta_2(-QR+R\alpha+\alpha\theta\delta_1)}{N(Q+\alpha+\mu+\delta_1)L(R+\mu+\theta\delta_1)}, \frac{\beta\eta_1}{N(R+\mu+\theta\delta_1)} - \frac{R\beta\eta_2}{NL(R+\mu+\theta\delta_1} , \frac{\beta\eta_2}{NL}, (0,0,0), (0,0,0)$$

Finding the eigen values of FV^{-1} we obtain;
X_1= 0
X_2= 0

$$X_3 = \frac{\beta}{N(Q+\alpha+\mu+\delta_1)} + \frac{Q\beta\eta_1}{N(Q+\alpha+\mu+\delta_1)(R+\mu+\theta\delta_1)} + \frac{\beta\eta_2(-QR+R\alpha+\alpha\mu+\alpha\theta\delta_1)}{N(Q+\alpha+\mu+\delta_1)(\mu+\omega+\delta_2)(R+\mu+\theta\delta_1)}$$

which is the spectral radius/dominant eigen value [R_O]. In general, a value of $R_0 < 1$ implies that each individual is only able to infect less than one individual on average, so that the disease will die out hence the disease free equilibrium will be locally and globally asymptotically stable. A value of $R_0 > 1$ implies that each individual is able to infect more than one individual on average and the disease is expected to persist in the population.

2.7. Existence of Endemic Equilibrium Point

For the sake of analysis let

$$\begin{aligned} \Omega_1 &= V_{max}\frac{A_L}{K_M+A_L}I_c \\ \Omega_2 &= -(\mu+\alpha+\delta_1+\Omega_1) \\ \Omega_3 &= V_{max}\frac{A_H}{K_M+A_H} \\ \Omega_4 &= \mu+\theta\delta_1+\Omega_3 \\ \Omega_5 &= \delta_2+\mu+\omega \\ \Omega_6 &= \mu+\phi \end{aligned}$$

our new equations reduces to:

$$\frac{dS}{dt} = \pi + \phi R - \mu S - \lambda S \tag{6}$$
$$\frac{dI_c}{dt} = \lambda S - \Omega_2 I_c \tag{7}$$
$$\frac{dI_{cr}}{dt} = \Omega_1 I_c - \Omega_4 I_{cr} \tag{8}$$
$$\frac{dT_c}{dt} = \Omega_3 I_{cr} + \alpha I_c - \Omega_5 T_c \tag{9}$$
$$\frac{dR}{dt} = \omega T_c - \Omega_6 R \tag{10}$$
$$\tag{11}$$

Our new expression for reproduction number is given as:

$$R_0^* = \frac{S^0\beta}{N\Omega_2} + \frac{S^0\beta\eta_1\Omega_1}{N\Omega_2\Omega_5} + \frac{S^0\alpha\beta\eta_2}{N\Omega_2\Omega_5} + \frac{S^0\beta\eta_2\Omega_1\Omega_3}{N\Omega_2\Omega_4\Omega_5}$$

Solving reduced equations in terms of λ we obtain;

$$T_c = -\frac{\pi\lambda(\Omega_1\Omega_3 + \alpha\Omega_4)\Omega_6}{\lambda\phi\omega\Omega_1\Omega_3 + \Omega_4(\alpha\lambda\phi\omega - (\lambda+\mu)\Omega_2\Omega_5\Omega_6)}$$
$$I_{cr} = -\frac{\pi\lambda\Omega_1\Omega_5\Omega_6}{\lambda\phi\omega\Omega_1\Omega_3 + \Omega_4(\alpha\lambda\phi\omega - (\lambda+\mu)\Omega_2\Omega_5\Omega_6)}$$
$$I_c = -\frac{\pi\lambda\Omega_4\Omega_5\Omega_6}{\lambda\phi\omega(\Omega_1\Omega_3 + \alpha\Omega_4) + (\lambda+\mu)\Omega_2\Omega_4\Omega_5\Omega_6)}$$
$$S = -\frac{\pi\Omega_2\Omega_4\Omega_5\Omega_6}{\lambda\phi\omega(\Omega_1\Omega_3 + \alpha\Omega_4) + (\lambda+\mu)\Omega_2\Omega_4\Omega_5\Omega_6)}$$
$$R = -\frac{\pi\lambda\omega(\Omega_1\Omega_3 + \alpha\Omega_4)}{\lambda\phi\omega\Omega_1\Omega_3 + \Omega_4(\alpha\lambda\phi\omega - (\lambda+\mu)\Omega_2\Omega_5\Omega_6)}$$

by substituting force of infection, we have;

$$\lambda(1 + \frac{\pi\beta(\eta_1(\Omega_1\Omega_3 + \alpha\Omega_4) + (\eta_1\Omega_1 + \Omega_4)\Omega_5)\Omega_6}{N\lambda\phi\omega\Omega_1\Omega_3 + N\Omega_4(\alpha\lambda\phi\omega - (\lambda+\mu)\Omega_2\Omega_5\Omega_6)}) = 0$$

Case 1: either $\lambda = 0$ which correspond to disease free equilibrium point.
or
Case 2:

$$1 + \frac{\pi\beta(\eta_2(\Omega_1\Omega_3 + \alpha\Omega_4) + (\eta_1\Omega_1 + \Omega_4)\Omega_5)\Omega_6}{N\lambda\phi\omega\Omega_1\Omega_3 + N\Omega_4(\alpha\lambda\phi\omega - (\lambda+\mu)\Omega_2\Omega_5\Omega_6)} = 0$$

which corresponds to E.E.P. That is

$$\lambda = \frac{(\pi\beta\eta_2(\Omega_1\Omega_3 + \alpha\Omega_4) + (\pi\beta\eta_1\Omega_1 + (\pi\beta - N\mu\Omega_2)\Omega_4)\Omega_5)\Omega_6}{-N\phi\omega(\Omega_1\Omega_3 + \alpha\Omega_4) + N\Omega_2\Omega_4\Omega_5\Omega_6}$$

expressing λ in terms of R_o^*, we obtain;

$$\lambda = \frac{(-\pi R_o^* + S^0\mu)\Omega_2\Omega_4\Omega_5\Omega_6(M)}{S^0(\phi\omega\Omega_1\Omega_3 + \Omega_4(\alpha\phi\omega - \Omega_2\Omega_5\Omega_6))N)}$$

Case 1: suppose $N > 0$ then $M > 0$ for $\lambda > 0$ which implies that

$$\begin{aligned} -\pi R_0^* + S^0\mu &> 0 \\ but & \\ S^0 &= \frac{\pi}{\mu} \\ -\pi R_0^* + \pi &> 0 \\ \pi(-R_0^* + 1) &> 0 \end{aligned}$$

but $\pi \neq 0$, $-R_0^* + 1 > 0$, $R_0^* < 1$ which show that the disease will die out hence disease free equilibrium point exist.
.
Case 2:
If $N < 0$, then $M <$ for $\lambda > 0$

$$\begin{aligned} -\pi R_0^* + S^0\mu &< 0 \\ S^0 &= \frac{\pi}{\mu} \\ -\pi R_0^* + \pi &< 0 \\ \pi(-R_0^* + 1) &< 0 \end{aligned}$$

but $\pi \neq 0$, $-R_0^* < -1$, $R_0^* > 1$ which show that the disease will persist hence endemic equilibrium point (E.E.P) exist and this complete the proof. The exact E.E.P are determined by substituting λ in the reduced equation to obtain;

$$\begin{aligned} R =& -\frac{\beta\pi(R_0^* - 1)(\eta_2\Omega_1\Omega_3 + \alpha\Omega_4) + (\eta_1\Omega_1 + \Omega_4)\Omega_5)\Omega_6}{NR_0^*(\phi\omega\Omega_1\Omega_3 + \Omega_4(\alpha\phi\omega - \Omega_2\Omega_5\Omega_6))} \\ S =& \frac{1}{R_0^*}S^0 \\ I_c =& -\frac{\pi(R_0^* - 1)\Omega_4\Omega_5\Omega_6}{R_0^*(\phi\omega\Omega_1\Omega_3 + \Omega_4(\alpha\phi\omega - \Omega_2\Omega_5\Omega_6))} \\ I_{cr} =& -\frac{\pi(R_0^* - 1)\Omega_1\Omega_5\Omega_6}{R_0^*(\phi\omega\Omega_1\Omega_3 + \Omega_4(\alpha\phi\omega - \Omega_2\Omega_5\Omega_6))} \\ T_c =& -\frac{\pi(R_0^* - 1)(\Omega_1\Omega_3 + \alpha\Omega_4)\Omega_6}{R_0^*(\phi\omega\Omega_1\Omega_3 + \Omega_4(\alpha\phi\omega - \Omega_2\Omega_5\Omega_6))} \end{aligned}$$

the endemic equilibrium point is numerically illustrated in figure 2.

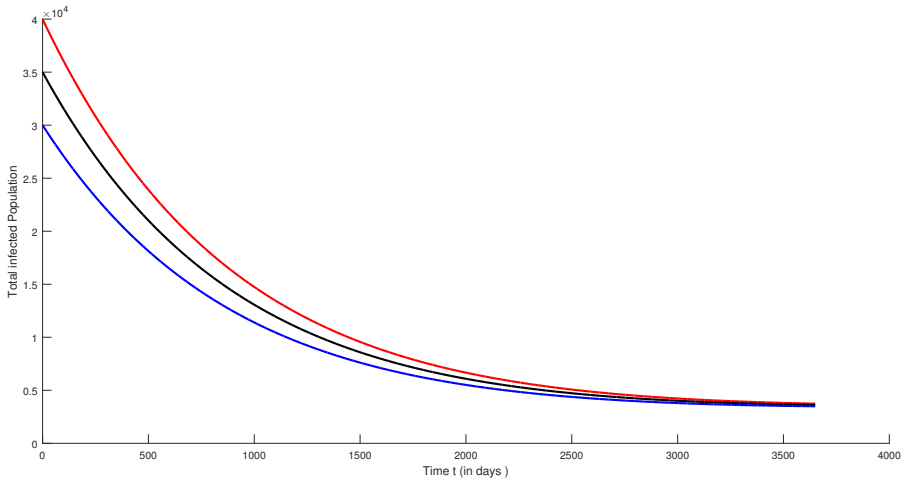

Figure 2. *Total cholera infected individuals with time.(EEP).*

2.8. Local Stability of the disease free equilibrium point (D.F.E)

Theorem:
The D.F.E is locally asymptotically stable whenever $R_0^* < 1$
Proof:
Determining jacobian matrix of our reduced equations as follows;

$$\begin{aligned} f_1 =& \pi + \phi R - \mu S - \lambda S \\ f_2 =& \lambda S - \Omega_2 I_c \\ f_3 =& \Omega_1 I_c - \Omega_4 I_{cr} \\ f_4 =& \Omega_3 I_{cr} + \alpha I_c - \Omega_5 T_c \\ f_5 =& \omega T_c - \Omega_6 R \end{aligned}$$

Determining the jacobian matrix at D.F.E we obtain;

$$\begin{bmatrix} -\mu & -\beta & -\beta\eta_1 & -\beta\eta_2 & \phi \\ 0 & \beta - \Omega_2 & \beta\eta_1 & \beta\eta_2 & 0 \\ 0 & \Omega_1 & -\Omega_4 & 0 & 0 \\ 0 & \alpha & \Omega_3 & -\Omega_5 & 0 \\ 0 & 0 & 0 & \omega & -\Omega_6 \end{bmatrix}$$

through inspection we obtain following eigen values which are negatives

$\chi_1 = -\mu$
$\chi_2 = -\Omega_6$
the matrix reduces to;

$$\begin{bmatrix} \beta - \Omega_2 & \beta\eta_1 & \beta\eta_2 \\ \Omega_1 & -\Omega_4 & 0 \\ \alpha & \Omega_3 & -\Omega_5 \end{bmatrix}$$

we shall determine signs of the remaining eigen values using Routh-Hurwitz criterion. The characteristic function $|A - X_i I| = 0$, with i=3,4,5

$X_i^3 + X_i^2\Omega_2 - \beta X_i^2 + X_i^2\Omega_4 + X_i^2\Omega_5 - \alpha\beta\eta_2 X_i - \beta\eta_1 X_i\Omega_1 - \beta\eta_2\Omega_1\Omega_3 - \alpha\beta\eta_2\Omega_4 - \beta X_i\Omega_4 + X_i\Omega_2\Omega_4 - \beta X_i\Omega_5 - \beta\eta_1\Omega_1\Omega_5 - X_i\Omega_2\Omega_5 - \beta\Omega_4\Omega_5 + X_i\Omega_4\Omega_5 + \Omega_2\Omega_4\Omega_5$

by Routh-Hurwitz criterion for determining the negatives real signs of the eigen values of the cubic polynomial are;

$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$ with conditions:

$a_1 > 0, a_1 a_2 > a_3 > 0$

from the characteristic polynomial the values of a_1, a_2 and a_3 expressed in terms of R_0^* are;

$a_1 = \Omega_4 + \Omega_5 + \Omega_2(1 - \frac{NR_0^*\Omega_4\Omega_5}{S^0\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+S^0(\eta_1\Omega_1+\Omega_4)\Omega_5)})$

$a_2 = \Omega_2\Omega_4 + \Omega_2\Omega_5 - \frac{NR_0^*\alpha\eta_2\Omega_4\Omega_5}{S^0\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+S^0(\eta_1\Omega_1+\Omega_4)\Omega_5} - \frac{NR_0^*\eta_1\Omega_1\Omega_2\Omega_4\Omega_5}{S^0\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+S^0(\eta_1\Omega_1+\Omega_4)\Omega_5} - \frac{NR_0^*\Omega_2\Omega_4\Omega_5^2}{S^0\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+S^0(\eta_1\Omega_1+\Omega_4)\Omega_5}$

$$a_3 = \Omega_2\Omega_4\Omega_5 - \frac{NR_0^*\eta_2\Omega_1\Omega_2\Omega_3\Omega_4\Omega_5}{S^0\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+S^0(\eta_1\Omega_1+\Omega_4)\Omega_5} - \frac{NR_0^*\alpha\eta_2\Omega_2\Omega_4^2\Omega_5}{S^0\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+S^0(\eta_1\Omega_1+\Omega_4)\Omega_5} - \frac{NR_0^*\eta_1\Omega_1\Omega_2\Omega_4\Omega_5^2}{S^0\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+S^0(\eta_1\Omega_1+\Omega_4)\Omega_5} - \frac{NR_0^*\Omega_2\Omega_4^2\Omega_5^2}{S^0\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+S^0(\eta_1\Omega_1+\Omega_4)\Omega_5}$$

the condition necessary for a_1 to be positive

$$R_0^* < \frac{S^0(\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+(\eta_1\Omega_1+\Omega_4)\Omega_5}{N\Omega_4\Omega_5)}$$

$R_0^* = (NS^0\Omega_2\Omega_4\Omega_5(\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+(\eta_1\Omega_1+\Omega_4)\Omega_5)(\eta_1\Omega_1(\Omega_2+\Omega_4)+(\Omega_4+\Omega_5)(2\Omega_2+\Omega_4+\Omega_5)+\eta_1(-\Omega_1\Omega_3+\alpha(\Omega_2+\Omega_5))) - \sqrt{(N^2X^2\Omega_2^2\Omega_4^2\Omega_5^2(\eta_2\Omega_3+\alpha\Omega_4)+(\eta_1\Omega_1+\Omega_4)^2((\Omega_4^2+\eta_1\Omega_1(\Omega_2+\Omega_4)-\Omega_5^2)^2+\eta_2^2(\Omega_1\Omega_3-\alpha(\Omega_2+\Omega_5)^2+2\eta_2(\eta_1\Omega_1(\Omega_2+\Omega_4)(-\Omega_1\Omega_3+\alpha(\Omega_2+\Omega_5))-(\Omega_4+\Omega_5)(\alpha(\Omega_4-\Omega_5)(\Omega_2+\Omega_5)+\Omega_1\Omega_3(2\Omega_2+\Omega_4+\Omega_5)))))))/(2N^2\Omega_2^2\Omega_4^2\Omega_5^2(\alpha\eta_2+\eta_1\Omega_1+\Omega_4+\Omega_5))$

$R_0^* = (NS^0\Omega_2\Omega_4\Omega_5(\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+(\eta_1\Omega_1+\Omega_4)\Omega_5)(\eta_1\Omega_1(\Omega_2+\Omega_4)+(\Omega_4+\Omega_5)(2\Omega_2+\Omega_4+\Omega_5)+\eta_2(-\Omega_1\Omega_3+\alpha(\Omega_2+\Omega_5))) + \sqrt{(N^2(S^0)^2\Omega_2^2\Omega_4^2\Omega_5^2(\eta_2(\Omega_1\Omega_3+\alpha\Omega_4)+(\eta_1\Omega_1+\Omega_4)\Omega_5)^2((\Omega_4^2+\eta_1\Omega_1(\Omega_2+\Omega_4)-\Omega_5^2)^2+\eta_2^2(\Omega_1\Omega_3-\alpha(\Omega_2+\Omega_5))^2+2\eta_2(\eta_1\Omega_1(\Omega_2+\Omega_4)(-\Omega_1\Omega_3+\alpha(\Omega_2+\Omega_5)-(\Omega_4+\Omega_5)(\alpha(\Omega_4-\Omega_5)(\Omega_2+\Omega_5)+\Omega_1\Omega_3(2\Omega_2+\Omega_4+\Omega_5)))))))/(2N^2\Omega_2^2\Omega_4^2\Omega_5^2(\alpha\eta_2+\eta_1\Omega_1+\Omega_4+\Omega_5)))$

2.9. Global Stability of the disease free equilibrium point (D.F.E)

The global stability of disease free equilibrium is investigated using Metzler matrix stability method proposed by [14]

$$\frac{dX}{dt} = F(X, Z) \tag{12}$$

$$\frac{dZ}{dt} = G(X, Z), G(X, 0) = 0 \tag{13}$$

where:$X = (S, R) \in R_+^2$ denotes noninfectious cholera compartments and $Z = (I_c, I_{cr}, T_c) \in R_+^3$ denotes the infectious cholera compartment $E_0 = (X^*, 0)$ represents the disease free equilibrium of the system if this point satisfies following condition:

i.$\frac{dX}{dt} = F(X, 0)$, where X^* is globally asymptotically stable.
ii.$\frac{dZ}{dt} = D_Z G(X, 0)Z - G(X, Z) \geq 0$ for all $(X, Z) \in \Omega$, then we can conclude that E_0 is locally asymptotically stable if the following theorems holds:

Theorem:
The equilibrium point $E_0(X^*, 0)$ of the system (12-13) is globally asymptotically stable if $R_0^* \leq 1$ and the conditions (i) and (ii) are satisfied, otherwise unstable.

proof:
Let X=(S,R) and Z=(I_c, I_{cr}, T_c), be the new variables and the sub systems of the system model (1-5). From equation (12-13) two vector functions G(X,Z) and F(X,Z) we consider reduced systems,

F(X,0)= $\begin{pmatrix} \pi - \mu S \\ 0 \end{pmatrix}$

It is noted that this is an asymptomatic dynamics system indepedence of the initial condition in Ω; therefore, the convergence of the solutions of the reduced system (12-13) is global in Ω by computing:
$\hat{G}(XZ) = D_Z G(X^*, 0)Z - G(XZ)$
$\hat{G}(X, Z) \geq 0$. Now let A=$D_Z G(X^*.0)$, which is the jacobian of $\hat{G}(X, Z)$ taken in (I_c, I_{cr}, T_c) and evaluated at $(X^*, 0)$, such that the matrix A is given by;

A= $\begin{bmatrix} \beta - \Omega_2 & \beta\eta_1 & \beta\eta_2 \\ \Omega_1 & -\Omega_4 & 0 \\ \alpha & \Omega_3 & -\Omega_5 \end{bmatrix}$

the values for $\hat{G}(X, Z)$ is given by matrix

AZ= $\begin{bmatrix} T_c\beta\eta_1 + I_{cr}\beta\eta_1 + I_c(\beta - \Omega_2) \\ I_c(\Omega_1) - I_{cr}\Omega_4 \\ I_c\alpha + I_{cr}\Omega_3 - T_c\Omega_5 \end{bmatrix}$

$\hat{G}(X, Z) = \begin{bmatrix} (1 - \frac{S}{N})\beta(I_c\eta_1 + T_c + I_{cr}\eta_2 \\ 0 \\ 0 \end{bmatrix}$

Therefore if $\hat{G}(X, Z) \geq 0$, then the disease free equilibrium, (E_0) is globally asymptotically stable otherwise it's unstable. Since $S \leq N$, $\frac{S}{N} \leq 1$, thus $G(X, Z) \geq 0$ for all $X, Z \in_+^3$, then, the disease free equilibrium will be globally asymptotically stable. It's clear that matrix A is an M-matrix since the off-diagonal elements of A are non-negative. Therefore, this proves that G.D.F.E is globally asymptotically stable. This completed the proof. This result show that cholera would die out whenever $R_0^* < 1$ irrespective of the initial conditions.

2.10. Bifurcation analysis

The bifurcation analysis can be explored using center manifold theorem [15]. The change of variables is made first for simplicity. Let S=y_1, $I_c = y_2$, $I_{cr} = y_3$, $T_c = y_4$ and $R = y_5$. Further, by using vector notation, y=$(y_1, y_2, y_3, y_4, y_5)$, the cholera model (6-11) was written in the form $\frac{dy}{dt} = F(y)$, with F=(p_1, p_2, p_3, p_4) as follows:

$$\dot{y_1} = p_1 = \pi + \phi y_5 - \mu y_1 - \beta \frac{(y_2 + \eta_1 y_3 + \eta_2 y_4)}{N} y_1 \tag{14}$$

$$\dot{y_2} = p_2 = \beta \frac{(y_2 + \eta_1 y_3 + \eta_2 y_4)}{N} y_1 - \Omega_2 y_2 \tag{15}$$

$$\dot{y_3} = p_3 = \Omega_1 y_2 + \alpha y_2 - \Omega_5 y_4 \tag{16}$$

$$\dot{y_4} = p_4 = \Omega_3 y_3 + \alpha y_2 - \Omega_5 y_4 \tag{17}$$

$$y_5 = \omega y_4 - \Omega_6 y_5 \tag{18}$$

$$\tag{19}$$

where, $\lambda^* = \beta \frac{(y_2+\eta_1 y_3+\eta_2 y_4)}{N})$. The method entails evaluating the jacobian of the system (14-19) at D.F.E, $E^0_* = (S^0_*, {I_{c*}}^0, {I_{cr*}}^0, {T_{c*}}^0, R^0_*) = (\frac{\pi}{\mu}, 0, 0, 0, 0)$, denoted by $J(E^0_*)$, we obtain

$$JE^0_* = \begin{bmatrix} -\mu & -\beta^* & -\beta^*\eta_1 & -\beta\eta_2 & \phi \\ 0 & \beta^* - \Omega_2 & \beta^*\eta_1 & \beta^*\eta_2 & 0 \\ 0 & \Omega_1 & -\Omega_4 & 0 & 0 \\ 0 & \alpha & \Omega_3 & -\Omega_5 & 0 \\ 0 & 0 & 0 & \omega & -\Omega_6 \end{bmatrix}$$

we consider the case where $R^*_0 = 1$. Suppose $\beta = \beta^*$ chosen as a bifurcation parameter then solving for β^* from $R^*_C = 1$ gives:
$\beta^* = \frac{N\Omega_2\Omega_4\Omega_5}{S^0(\eta_2\Omega_1\Omega_3 + \alpha\eta_2\Omega_4 + \eta_1\Omega_1\Omega_5 + \Omega_4\Omega_5)}$
The Jacobian of;
$\frac{dy}{dx} = F(y)$ at the disease free equilibrium point, with $\beta = \beta^*$, denoted by $J(E^0_*)$, has eigen values $(-\mu, -\Omega_6)$ the matrix reduces to.

$\begin{bmatrix} \beta^* - \Omega_2 & \beta^*\eta_1 & \beta^*\eta_2 \\ \Omega_1 & -\Omega_4 & 0 \\ \alpha & \Omega_3 & -\Omega_5 \end{bmatrix}$ in which one of the eigen values must be zero. Hence the centre manifold theorem is used to analyze dynamics of the model. The theorem by [14], considered the following general system of ordinary differential equations with a parameter β^*

$\frac{dy}{dx} = f(y, \beta^*), f : R^n \times R \longrightarrow R^n$ and $f \in C^2(R^2 \times R)$ where 0 is an equilibrium point of the system (that is, $f(y, \beta^*) \equiv 0$ and

1) $A = D_Y f(0, 0) = (\frac{\delta P_i}{\delta y_j(0,0)})$, is the linearization matrix of the system around the equilibrium 0 with β^* 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 u and a left eigenvector v corresponding to the zero eigenvalue. Let p_k be the kth component of p and

$$a = \sum_{k,ij=1}^{n} v_k u_i u_j \frac{\delta^2 p_k}{\delta y_i \delta \beta^*}(0, 0)$$

$$b = \sum_{k,ij=1}^{n} v_k u_i \frac{\delta^2 p_k}{\delta y_i \delta \beta^*}(0, 0)$$

then the local dynamics of the system around the equilibrium point (0,0) is totally determined by the signs of a and b.
Particularly when:

i. $a > 0$ and $b > 0$, when $\beta^* < 0$ with $|\beta^*| << 1, (0, 0)$, is locally asymptotically stable and there exists a positive unstable equilibrium; $0 < \beta^* << 1, (0, 0)$ is unstable and there exists a negative and locally asymptotically stable equilibrium.
ii. $a < 0$ and $b < 0$ when $\beta^* < 0$ with $|\beta| << 1, (0, 0)$, is unstable; when $0 < \beta << 1, (0, 0)$ is asymptotically stable and there exists a positive unstable equilibrium.
iii. $a < 0$ and $b > 0$, when $\beta^* < 0$ is unstable, and there exists a negative and locally asymptotically stable equilibrium; when $0 < \beta << 1, (0, 0)$ is stable and there exists a positive unstable equilibrium.
iv $a < 0$ and $b > 0$, when β^* changes from negative to positive, (0,0) changes its stability from stable to unstable. Correspondingly a negative equilibrium becomes positive and locally asymptotically stable.

$a < 0$ and $b > 0$, then a backward bifurcation occurs at $\beta^* = 0$ [16]. Jacobian $[J(E^0_*)]$ at $\beta = \beta^*$ (denoted by J^*_β) has a right eigen vector given by u= $[u_1, u_2, u_3, u_4, u_5]^T$, let $u_2 = u_2 > 0$, then

$$
\begin{aligned}
u_1 =& \frac{-\beta^* u_1 - \beta^* \eta_1 u_3 - \beta^* \eta_2 u_4 + \phi u_5}{u} < 0 \\
u_2 =& \frac{-(\beta^* \eta_1 u_3 + \beta^* \eta_2 u_4)}{\beta - \Omega_2} > 0 \\
u_3 =& \frac{\Omega_1 u_2}{\Omega_4} > 0 \\
u_4 =& \frac{\alpha u_2 + \Omega_3 u_3}{\alpha} > 0 \\
u_5 =& \frac{\omega u_4}{\Omega_6} > 0
\end{aligned}
$$

Further, J^*_β has a left eigen vectors v=$[v_1, v_2, v_3, v_4, v_5]$ let $v_1 = v_1 = 0$

$$
\begin{aligned}
v_2 =& -\frac{(v_3 \Omega_1 + v_4 \alpha)}{\beta^* - \Omega_2} > 0 \\
v_3 =& \frac{\beta^* \eta_1 v_2 + v_4 \Omega_4}{\Omega_4} > 0 \\
v_4 =& \frac{\beta^* \eta_2 v_2 + v_5 \omega}{\Omega_5} > 0 \\
v_5 =& \frac{\phi}{\Omega_6} > 0
\end{aligned}
$$

$$\begin{aligned}
\frac{dp_1}{dy_1} &= -\mu - \frac{\beta(y_2+\eta_1 y_3+\eta_2 y_4)}{N}\\
\frac{d^2p_1}{dy_1dy_2} &= -\frac{\beta}{N}\\
\frac{dp_1}{dy_1} &= -\mu - \frac{\beta(y_2+\eta_1 y_3+\eta_2 y_4)}{N}\\
\frac{d^2p_1}{dy_1dy_3} &= -\frac{\beta\eta_1}{N}\\
\frac{dp_1}{dy_1} &= -\mu - \frac{\beta(y_2+\eta_1 y_3+\eta_2 y_4)}{N}\\
\frac{d^2p_1}{dy_1dy_4} &= -\frac{\beta\eta_2}{N}\\
\frac{dp_2}{dy_1} &= \frac{\beta(y_2+\eta_1 y_3+\eta_2 y_4)}{N}\\
\frac{d^2p_2}{dy_1dy_2} &= \frac{\beta}{N}\\
\frac{dp_2}{dy_1} &= \frac{\beta(y_2+\eta_1 y_3+\eta_2 y_4)}{N}\\
\frac{d^2p_1}{dy_1dy_3} &= \frac{\beta\eta_1}{N}\\
\frac{dp_1}{dy_1} &= \frac{\beta(y_2+\eta_1 y_3+\eta_2 y_4)}{N}\\
\frac{d^2p_1}{dy_1dy_4} &= \frac{\beta\eta_2}{N}
\end{aligned}$$

$a = v_1[-2u_1u_2\frac{\beta}{N} - 2u_1u_3\frac{\beta\eta_1}{N} - 2u_1u_4\frac{\beta\eta_2}{N}] + v_2[2u_1u_2\frac{\beta}{N} + 2u_1u_3\frac{\beta\eta_1}{N} + 2u_1u_4\frac{\beta\eta_2}{N}]$
but $v_1 = 0$

$$\begin{aligned}
\frac{dp_1}{dy_1} &= -\mu - \frac{\beta(y_2+\eta_1 y_3+\eta_2 y_4)}{N}\\
\frac{d^2p_1}{dy_1d\beta^*} &= -\frac{(y_2+\eta_1 y_3+\eta_2 y_4)}{N}
\end{aligned}$$

at disease free equilibrium(0,0), $y_2 = y_3 - y_4 = 0$

$$\begin{aligned}
\frac{dp_1}{dy_2} &= -\frac{\beta y_1}{N} \\
\frac{d^2p_1}{dy_2 d\beta^*} &= -\frac{y_1}{N} \\
\frac{dp_1}{dy_3} &= -\frac{\eta_1 \beta y_1}{N} \\
\frac{d^2p_1}{dy_3 d\beta^*} &= -\frac{\eta_1 y_1}{N} \\
\frac{dp_1}{dy_4} &= -\frac{\beta \eta_2 y_1}{N} \\
\frac{d^2p_1}{dy_4 d\beta^*} &= -\frac{\eta_2 y_1}{N} \\
\frac{dp_2}{dy_1} &= \frac{\beta(y_2 + \eta_1 y_3 + \eta_2 y_4)}{N} \\
\frac{d^2p_1}{dy_1 d\beta^*} &= \frac{(y_2 + \eta_1 y_3 + \eta_2 y_4)}{N}
\end{aligned}$$

at D.F.E(0,0), $y_2 = y_3 = y_4 = 0$

$$\begin{aligned}
\frac{dp_2}{dy_2} &= \frac{\beta}{N} - \Omega_2 \\
\frac{d^2p_1}{dy_2 d\beta^*} &= \frac{1}{N} \\
\frac{dp_2}{dy_3} &= \frac{\beta \eta_1}{N} \\
\frac{d^2p_1}{dy_3 d\beta^*} &= \frac{\eta_1}{N} \\
\frac{dp_2}{dy_4} &= \frac{\beta \eta_2}{N} \\
\frac{d^2p_1}{dy_4 d\beta^*} &= \frac{\eta_2}{N}
\end{aligned}$$

$b = v_1[-u_2\frac{y_1}{N} - u_3\frac{\eta_1 y_1}{N} - u_4\frac{\eta_2 y_1}{N}] + v_2[\frac{u_2}{N} + \frac{u_3\eta_1}{N} + \frac{u_4\eta_2}{N}]$

but $v_1 = 0$, $b > 0$. Hence $a < 0$ and $b > 0$, when $\beta^* < 0$ with $|\beta^*| <<, (0,0)$ is unstable and there exists a negative and locally asymptotically stable equilibrium; when $0 < \beta^* << 1, (0,0)$ is stable and there exists a positive unstable equilibrium. The direction of the bifurcation of system (3.3.1) at $R_0 = 1$ is forward. Since the bifurcation parameter changes from negative to positive and the disease-free equilibrium changes its stability from negative to positive. Therefore, there exists a positive unstable equilibrium and locally asymptomatic stable equilibrium.

2.11. Global stability analysis of the Endemic Equilibrium Point

For the system of reduced equations;

$$\frac{dS}{dt} = \pi + \phi R - \mu S - \lambda S \tag{20}$$
$$\frac{dI_c}{dt} = \lambda S - \Omega_2 I_c \tag{21}$$
$$\frac{dI_{cr}}{dt} = \Omega_1 I_c - \Omega_4 I_{cr} \tag{22}$$
$$\frac{dT_c}{dt} = \Omega_3 I_{cr} + \alpha I_c - \Omega_5 T_c \tag{23}$$
$$\frac{dR}{dt} = \omega T_c - \Omega_6 R \tag{24}$$
$$\tag{25}$$

the control reproduction number(R_o^*), the force of infection (λ^*), D.F.E $E^0 = (S^0, I_c^0, I_{cr}^0, T_c^0, R^0) = (\frac{\pi}{\mu}, 0, 0, 0, 0)$ and E.E.P, $E^* = (S^*, I_c^*, I_{cr}^*, T_c^*, R^*)$ of the system (20-25) were given by;

$$R_0^* = \frac{S^0\beta}{N\Omega_2} + \frac{S^0\beta\eta_1\Omega_1}{N\Omega_2\Omega_5} + \frac{S^0\alpha\beta\eta_1}{N\Omega_2\Omega_5} + \frac{S^0\beta\eta_2\Omega_1\Omega_3}{N\Omega_2\Omega_4\Omega_5}$$

and system of equation in (6-11). We propose following Lyapunov function
$K(S, I_c, I_{cr}, T_c, R) = S - S^* - S^* Ln\frac{S}{S^*} + y_1(I_c - I_c^* - I_c^* Ln\frac{I_c}{I_c^*}) + y_2(I_{cr} - I_{cr}^* - I_{cr}^* Ln\frac{I_{cr}}{I_{cr}^*}) + y_3(T_c - T_c^* - T_c^* Ln\frac{T_c}{T_c^*}) + y_4(R - R^* - R^* Ln\frac{R}{R^*})$

where y_1, y_2, y_3, y_4 were positive constant to be determined. The Lyapunov function $K(S, I_c, I_{cr}, T_c, R)$ satisfies the conditions $K(S^*, I_c^*, I_{cr}^*, T_c, R) = 0$ and $K(S, I_c, I_{cr}, T_c, R) > 0$, hence it's positive definate for;

$$\frac{dk(S, I_c, I_{cr}, T_c, R)}{dt}$$

to be negative definate, it must satisfy,

$$\frac{dk(S^*, I_c^*, I_{cr}^*, T_c^*, R^*)}{dt} = 0$$

and

$$\frac{dk(S^*, I_c^*, I_{cr}^*, T_c^*, R^*)}{dt} < 0$$

the E.E.P, $E^* = (S^*, I_c^*, I_{cr}^*, T_c^*, R^*)$ for the system satisfies,

$$\pi = \mu S^{**} + \lambda^{**} S^{**} - \phi R^{**} \tag{26}$$
$$\lambda^{**} S^{**} = \Omega_2 I_c^{**} \tag{27}$$
$$\Omega_4 I_{cr}^* * = \Omega_1 I_c^* * + \alpha I_c \tag{28}$$
$$\Omega_5 T_c^{**} = \Omega_3 I_{cr}^{**} + \alpha I_c^{**} \tag{29}$$
$$\Omega_6 R^{**} = \omega T_c^{**} \tag{30}$$

$dK(S, I_c, I_{cr}, T_c, R) = (1 - \frac{S^{**}}{S})(\frac{ds}{dt}) + y_1(1 - \frac{I_c^* *}{I_c})\frac{dI_c}{dt} + y_2(1 - \frac{I_{cr}^{**}}{dt})\frac{dI_{cr}}{dt} + y_3(1 - \frac{T_c^{**}}{T_c})\frac{dT_c}{dt} + y_4(1 - \frac{R^{**}}{R})\frac{dR}{dt}$
substituting for $\frac{dS}{dt}, \frac{dI_c}{dt}, \frac{dI_{cr}}{dt}, \frac{dT_c}{dt}, \frac{dR}{dt}$ in the equation (26-30) to obtain

$dK(S,I_c,I_{cr},T_c,R) = (1-\frac{S^{**}}{S})(\pi+\phi R-\mu S-\lambda S)+y_1(1-\frac{I_c^{**}}{I_c})(\lambda S-\Omega_2 I_c)+y_2(1-\frac{I_{cr}}{I_{cr}})(\Omega_1 I_c-\Omega_4 I_{cr})+y_3(1-\frac{T_c^{**}}{T_c})(\Omega_3 I_{cr}-\Omega_5 T_c)+y_4(1-\frac{R^{**}}{R})(\omega T_c-\Omega_6 R)$

$dK(S,I_c,I_{cr},T_c,R) =$
$\mu S^{**}+\lambda^{**}S^{**}-\phi R^{**}+\phi R-\mu S-\lambda S-\frac{S^{**}}{S}\mu S^{**}-\frac{S^{**}}{S}\lambda^{**}S^{**}+\frac{S^{**}}{S}\phi S^{**}-\frac{S^{**}}{S}\phi R+\frac{S^{*}*}{S}\mu S+\frac{S^{**}}{S}\lambda S+y_1\lambda S-y_1\Omega_2 I_c-\frac{I_c^{**}}{I_c}y_1\lambda S+y_1\frac{I_c^{**}}{I_c}\Omega_2 I_c+y_2\Omega_1 I_c-y_2\Omega_4 I_{cr}-\frac{I_{cr}}{I_{cr}}y_2\Omega_1 I_c-y_2\frac{I_{cr}}{I_{cr}}\alpha I_c+y_2\frac{I_{cr}}{I_{cr}}\Omega_4 I_{cr}+y_3\Omega_3 I_{cr}+y_3\alpha I_c-y_3\Omega_5 T_c-y_3\frac{T_c^{**}}{T_c}\Omega_3 I_{cr}-y_3\frac{T_c^{**}}{T_c}\alpha I_c+y_3\frac{T_c^{**}}{T_c}\Omega_5 T_c+y_4\omega T_c+y_4\Omega_6 R-y_4\frac{R^{**}}{R}\omega T_c+y_4\frac{R^{**}}{R}\Omega_6 R$

$\lambda=\frac{\beta(I_c+\eta_1 I_{cr}+\eta_2 T_c}{)}N=\frac{\beta I_c(s)}{N}+\frac{\eta_1 I_{cr}(s)}{N}+\frac{\eta_2 T_c(s)}{N}$
$I_c(s)=\frac{-\beta I_c(s)}{N}+\frac{y_1\beta I_c(s)}{N}$
$I_{cr}(s)=\frac{-\beta\eta_1 I_{cr}(s)}{N}+\frac{y_1\beta\eta_1 I_{cr}(s)}{N}$
$T_c(s)=\frac{-\beta\eta_2 T_c(s)}{N}+\frac{y_1\beta\eta_2 T_2(s)}{N}$
$dK(S,I_c,I_{cr},T_c,R)=\mu S^{**}+\lambda^{**}S^{**}-\phi S^{**}+\phi R-\mu S+I_c(\frac{-\beta}{N}+y_1\frac{\beta}{N})+I_{cr}(\frac{-\beta\eta_1}{N}+y_1\frac{\eta_1\beta}{N})+T_c(\frac{-\beta\eta_2}{N}+y_1\frac{\beta\eta_2}{N})-\frac{S^{**}}{S}\mu S^{**}-\frac{S^{**}}{S}\lambda^{**}S^{**}+\frac{S^{**}}{S}\phi S^{**}-S^{**}\phi R+S^{**}\mu+S^{*}*\lambda+I_c(-y_1\Omega_1+y_2\Omega_4+y_2\Omega_1+y_3\alpha)-\frac{I_c^{**}}{I}\lambda S+\frac{I_c^{*}*}{I}\lambda S+\frac{I_c^{*}*}{I}\Omega_2+I_{cr}(-y_2\Omega_4+y_3\Omega_3)-\frac{I_{cr}}{I_{cr}}\Omega_1 I_c-\frac{I_{cr}^{**}}{I_{cr}}\alpha I_c+I_{cr}\Omega_4+T_c(-y_3\Omega_5+y_4\omega)-y_3\frac{T_c^{**}}{T_c}\Omega_3 I_{cr}-y_3\frac{T_c^{**}}{T_c}\alpha I_c+y_3 T_c\Omega_5-y_4\Omega_6 R-y_4\frac{R^{**}}{R}\omega T_c+y_4 R^{**}\Omega_6$
let $I_c(s)=(\frac{-\beta}{N}+y_1\frac{\beta}{N})=0$
$I_c(s)\frac{\beta}{N}(y_1-1)=0$ but $I_c\neq 0, y_1-1=0, y_1=1$
$-y_1\Omega_1+y_2\Omega_4+y_2\Omega_1+y_3\alpha=0$
$-y_2\Omega_4+y_3\Omega_3=0$
$-y_3\Omega_5+y_4\omega=0$
$\phi R-y_4\Omega_6 R=0$
$R(\phi-y_4\Omega_6)=0$

but $R\neq 0$
$y_4=\frac{\phi}{\Omega_6}$
$-y_3\Omega_5+\frac{\phi}{\Omega_6}\omega=0$
$y_3=\frac{\phi\omega}{\Omega_5\Omega_6}$
$-y_2\Omega_4+\frac{\phi\omega\Omega_3}{\Omega_5\Omega_6}=0$
$y_2=\frac{\phi\omega\Omega_3}{\Omega_5\Omega_6\Omega_4}$

$dK(S,I_c,I_{cr},T_c,R) = \mu S^{**}+\lambda^{**}S^{**}-\phi R^{**}+\phi R-\mu S+I_c(s)(\frac{-\beta}{N}+y_1\frac{\beta}{N})+I_{cr}(\frac{-\beta\eta_1}{N}+y_1\frac{\eta_1\beta}{N})+T_c(s)(\frac{-\beta\eta_2}{N}+\frac{\beta\eta_2}{N})-\frac{S^{**}}{S}\mu S^{**}-\frac{S^{**}}{S}\lambda^{**}S^{**}+\frac{S^{**}}{S}\phi S^{**}-S^{**}\phi R+S^{**}\mu+S^{**}\lambda-\Omega_1+\frac{\phi\omega\Omega_3\Omega_1}{\Omega_5\Omega_6\Omega_4}+\frac{\phi\omega\alpha}{\Omega_5\Omega_6}-\frac{I_c^{**}}{I}\lambda S+\frac{I_c^{**}}{I}\Omega_2-\frac{\phi\omega\Omega_3}{\Omega_5\Omega_6}+\frac{\phi\omega\Omega_3}{\Omega_5\Omega_6}-\frac{I_{cr}^{**}}{I}\Omega_1 I_c-\frac{I_{cr}^{**}}{I_{cr}}\alpha I_c+I_{cr}^{**}\Omega_4-\frac{\phi\omega\Omega_5}{\Omega_5\Omega_6}+\frac{\phi\omega}{\Omega_6}-y_3\frac{T_c^{**}}{T_c}\Omega_3 I_{cr}-y_3\frac{\phi\omega T_c^{**}\Omega_3 I_{cr}}{\Omega_5\Omega_6 T_c}-\frac{\phi_c^{**}\alpha I_c}{\Omega_5\Omega_6}+\frac{\phi\omega T_c^{**}\Omega_5}{\Omega_5\Omega_6}-\phi R-\frac{\phi R^{**}\omega T_c}{\Omega_6 R}+\frac{\phi R^{**}\Omega_6}{\Omega_6}$

P= $\mu S^{**}+\lambda^{**}S^{**}+\phi R+I_c\frac{\beta}{N}+\frac{I_{cr}\eta_1\beta}{N}+\frac{T_c\beta\eta_2}{N}+\frac{S^{**}\phi S^{**}}{S}+S^{**}\mu+S^{**}\lambda+\frac{\phi\omega\Omega_3\Omega_1}{\Omega_5\Omega_6\Omega_4}+\frac{\phi\omega\alpha}{\Omega_5\Omega_6}+\frac{\phi\omega\Omega_3}{\Omega_5\Omega_6}+I_{cr}^{**}\Omega_4+\frac{\phi\omega}{\Omega_6}+\frac{\phi\Omega T_c^{**}\Omega_5}{\Omega_5\Omega_6}+\phi R^{**}$
Q= $-\phi S^{**}-\mu S-I_c\frac{\beta}{N}-\beta\frac{\eta_1}{N}I_{cr}-\beta\frac{\eta_2}{N}T_c-\frac{S^{**}}{S}\mu S^{**}-\frac{S^{**}}{S}\lambda^{**}S^{**}-S^{**}\phi R-\Omega_1-\frac{I^{**}}{I}\lambda S-\frac{\phi\omega\Omega_3}{\Omega_5\Omega_6}-\frac{I_{cr}^{**}\Omega_1 I_c}{I}-\frac{I_{cr}\alpha I_c}{I_{cr}}-\frac{\phi\omega\Omega_5}{\Omega_5\Omega_6}-\frac{\phi\omega T_c^{**}\Omega_3 I_{cr}}{\Omega_5\Omega_6 T_c}-\frac{\phi\omega T_c^{**}\Omega_3 I_{cr}}{\Omega_5\Omega_6 T_c}-\frac{\phi\omega T_c^{**}\alpha I_c}{\Omega_5\Omega_6}-\phi R-\frac{\phi R^{**}\omega T_c}{\Omega_6 R}$
Then $\frac{dK}{dt}=0$ holds only when $(S=S^{**},I_c=I_c^{**},I_{cr}=I_{cr},T_c=T_c^{**}$ and $R=R^{**}$ so the maximal compact invariant set in $(S;E;I)\in\sqcap$: $\frac{dv}{dt}=0$ is the singleton E_*^{**} using Lasalle's invariance principal $\frac{dL(S,I,A,R)}{dt}<0$ if and only if $P>Q$ [17]. This result show that cholera would persist whenever $P>Q$ irrespective of the initial conditions.

3. Simulation parameters of the model

In this section, the Runge-Kutta method is applied in the model equations and there after used to carry out numerical simulations by fourth order Runge-Kutta method in MatlabR2015a to study the dynamical behavior of the model state variables in the presence of model parameters. The Runge-Kutta method is a numerical method of solving an initial value problem of an ordinary differential equations. The numerical simulations are performed using the initial conditions and parameters in table 3 and the numerical results are presented graphically.

3.1. Normalized sensitivity analysis of basic reproduction numbers

Sensitivity analysis of parameters is carried out using the differential calculus. The analysis involves examining the parameter which affects the basic reproduction number most. It is commonly used to determine the robustness of model predictions to parameter values since there are errors in collecting data or pre-assumed parameter values.

Table 3. *Parameter values and initial conditions for the model estimated from Marsabit county, Kenya*

Parameter	Value	Source	Initial conditions	Value	Source
π	10/day	[18]	N	459 785	[19]
μ	0.0000913/day	[20]	S	361 251	[21]
λ	0.0000005	Estimated	I_c	72 202	[21]
δ_1	0.00000557	[22]	I_{cr}	3800	Estimated
α	0.98	[23]	T_c	11357	[21]
δ_2	0.0000000446	Estimated	R	11175	[21]
θ_1	1	Estimated			
ω	0.023/day	[24]			
A_L	0.00001	[6]			
A_H	0.0001	[6]			
K_M	1	Estimated			
β	0.0000029	Estimated			
V_{max}	0.01	Estimated			
ϕ	0.003	[24]			

Table 4. *Sensitivity indices*

Parameter	sinsitivity index
β	+1
η_2	+0.94437
Σ	-0.0000001
η_1	-0.00000000278
τ	-0.00000000097445
α	-0.0555
μ	-0.00382706
θ	-0.0000000000560306
δ_1	-0.000005683
χ	-1
δ_2	-0.000001824

3.2. The impact of cholera disease.

Figure 3: Susceptible population increases continously this is because they get recruited into the population through birth rate. The population then decreases hence forth untill it stabilizes due to infection of cholera and transition of these individuals to infected class. If the force of infection (λ) is increased the population increases and if its decreased the susceptible population decreases. The decrease in susceptible populations is also attributed by high cholera prevalence.

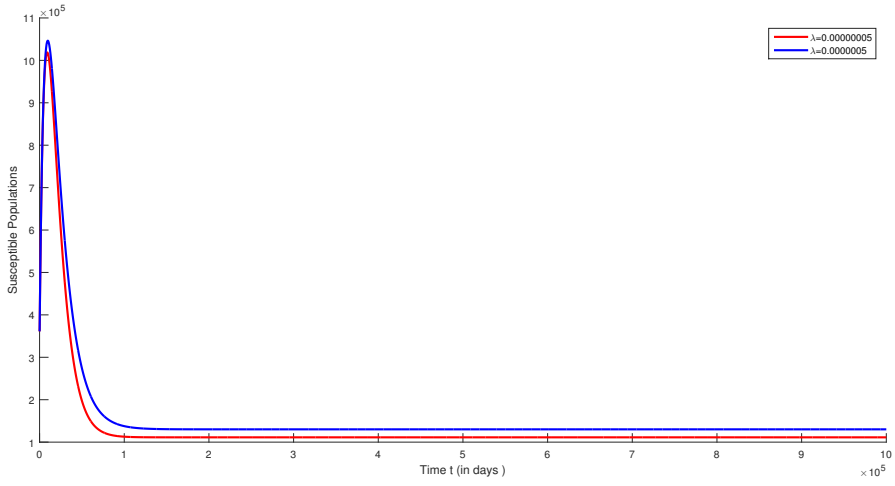

Figure 3. *population of susceptible individuals with Time*

Figure 4: Cholera infected individual decreases with time as some individuals are associated with problem of gastric

acid secretion hence developing achlorhydria condition and leaving the group, some cholera patient seek treatment for cholera and progress to treatment class while others die due to cholera. Variation in the force of infection show that if λ increase more people get infected with cholera and if it decreases less people get infection. Strategies should be made to reduce parameters incresing the force of infection.

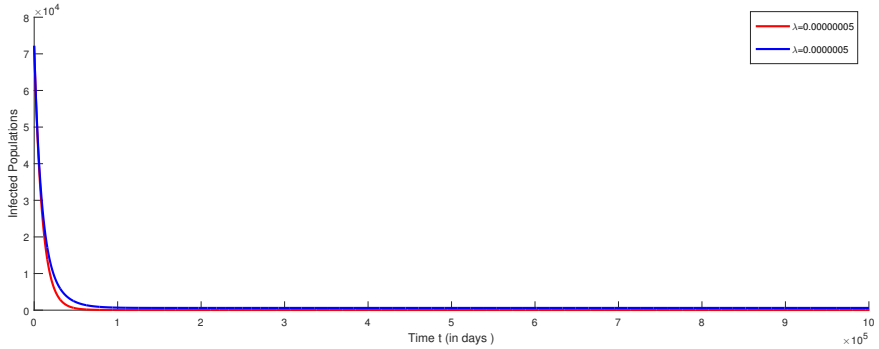

Figure 4. *Population of infected individuals with Time*

3.3. The implication of achlorhydria condition.

Figure 5: The population of achlohydria individuals decrease with time, as the achlorhydria condition is eliminated by initiating more production of hydrochloric acid in the digestive system or through treatment and these individuals either move to treatment class where they seek treatment for cholera or die due to cholera. Variation in the maximum acid concentration show that if it's high then the stomach will have a protective layer against *Vibrio cholerae* and development of induced achlohydria condition and if it's low then the stomach will be suitable for development of *Vibrio cholerae*.

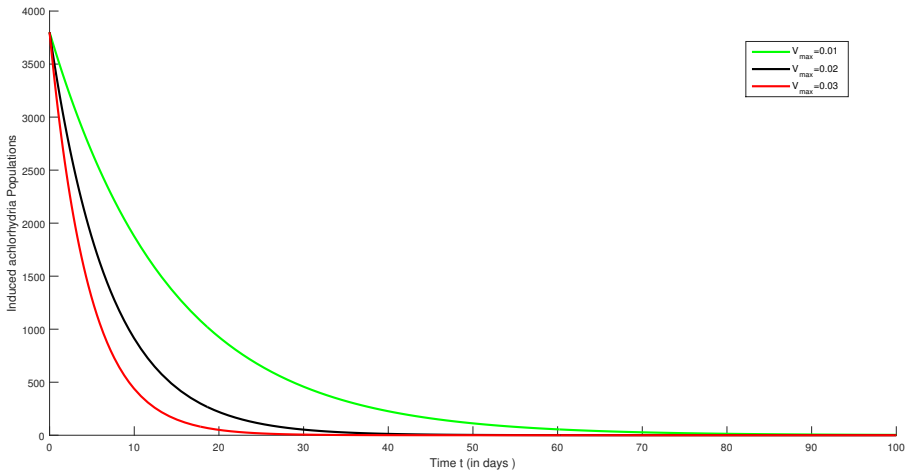

Figure 5. *Population of induced achlohydria individuals with Time*

3.4. Role of treatment.

Figure 6: The population increase since more individuals are leaving either infected class or achlorhydria class to seek for treatment of cholera. The population decrease untill it stabilizes as more people recover and progress

to recovered class. This class has less transmission and death rate due to cholera as it is assumed that treatment significantly reduces transmission and death rate.

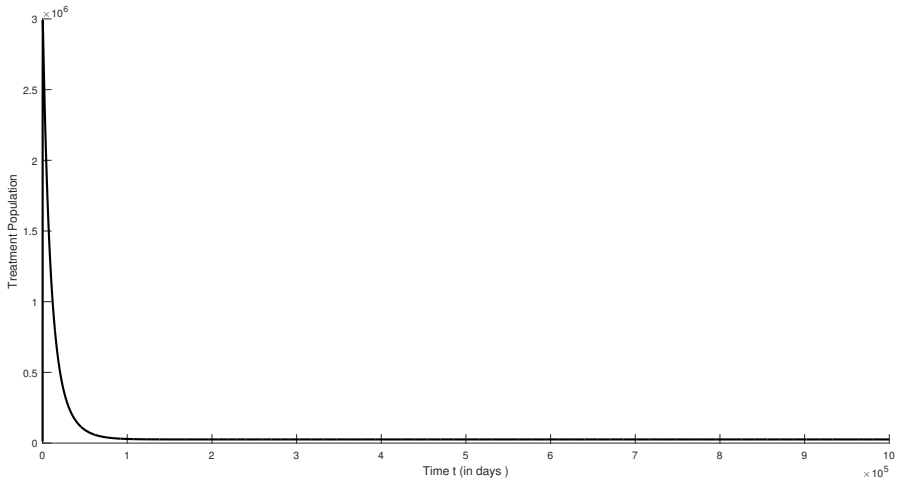

Figure 6. *Population of treatment individuals with Time*

Figure 7: The recovered individuals increase with time as more treated individuals recovers and join the class, then there is a decrease untill it stabilizes as the recovered individuals gain temporal immunity to the disease and join susceptible class.

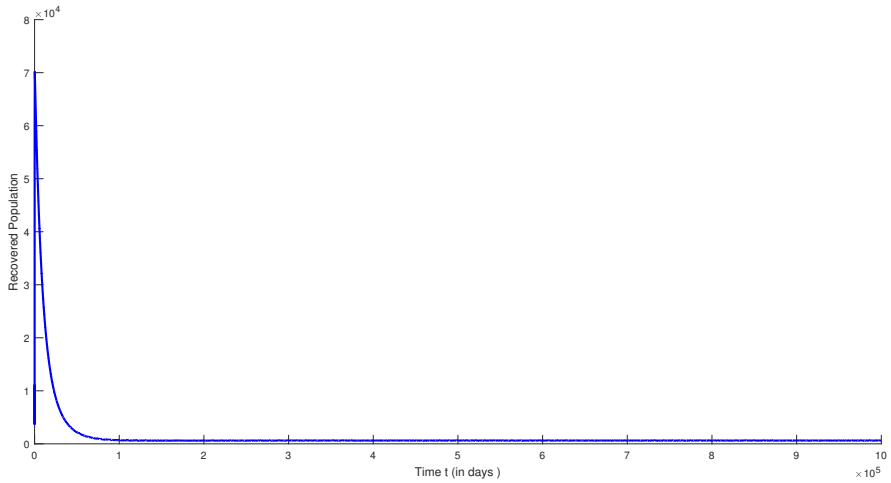

Figure 7. *Population of recovered individuals with Time*

3.5. Relationship between Infected individuals I_c, Induced achlorhydria population I_{cr} and Treated class (T_c)

Figure 8: It can be observed that I_{cr} and I_c are directly proportional to each other as the cholera infected individuals increases there is a significant increase in the number of cholera infected with induced achlorhydria individuals, as *Vibrio cholerae* induces this condition on individuals with problem of gastric acid secretion. Strategies should be targeted toward reducing cholera transmission and also people with problem of gastric acid secretions.

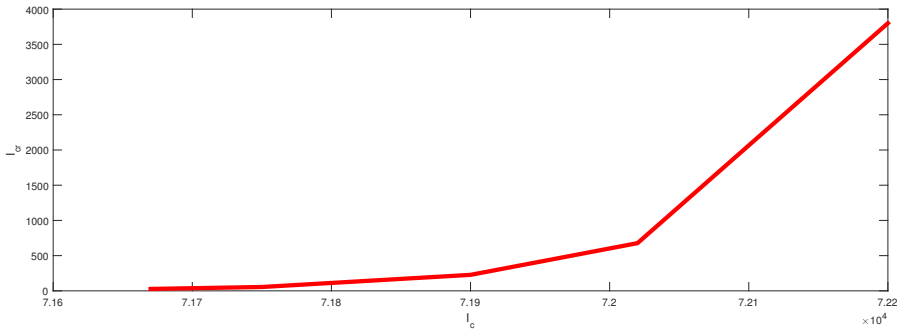

Figure 8. *Population of cholera infective against cholera infective and have induced achlorhydria*

Figure 9: The relationship between I_c and T_c is inversely proportional. I_c increases with time as T_c decreases with time as there is high cholera infection with low turn out for those seeking treatment. strategies should be targeted to reducing parameters leading to increase in I_c.

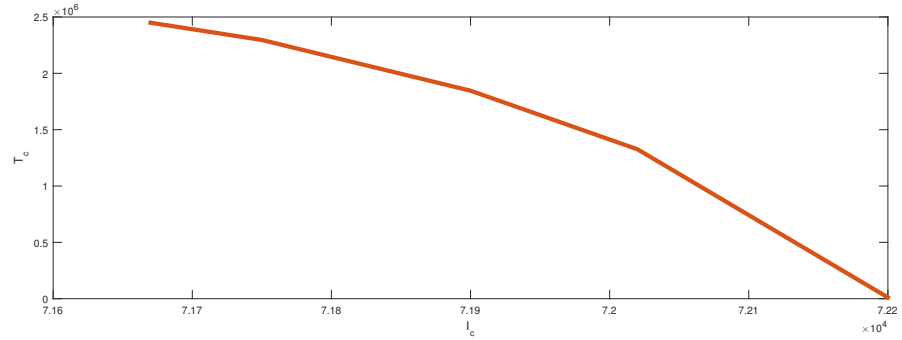

Figure 9. *Population of cholera infective against individuals seeking treatment for cholera.*

Figure 10: The relationship between I_{cr} and T_c is inversely proportional. I_{cr} increases with time as T_c decreases with time. strategies should be targeted toward reducing parameters leading to increase in I_{cr}.

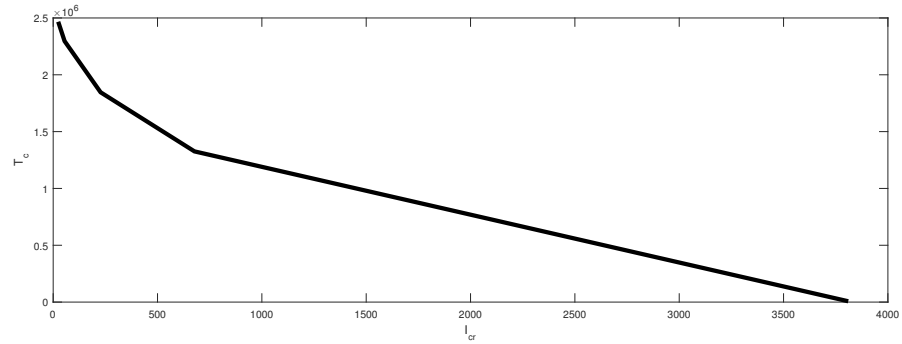

Figure 10. *Population of cholera infective with induced achlorhydria against those seeking treatment for cholera*

3.6. Figure 12 and 13 shows the impact of cholera on the total population without any intervention.

In Figure 12: Show the total population of individuals in absence of cholera disease, population increases gradually in absence of cholera disease. From the figure its evident that the population doubles after every ten years a case of Kenyan population.

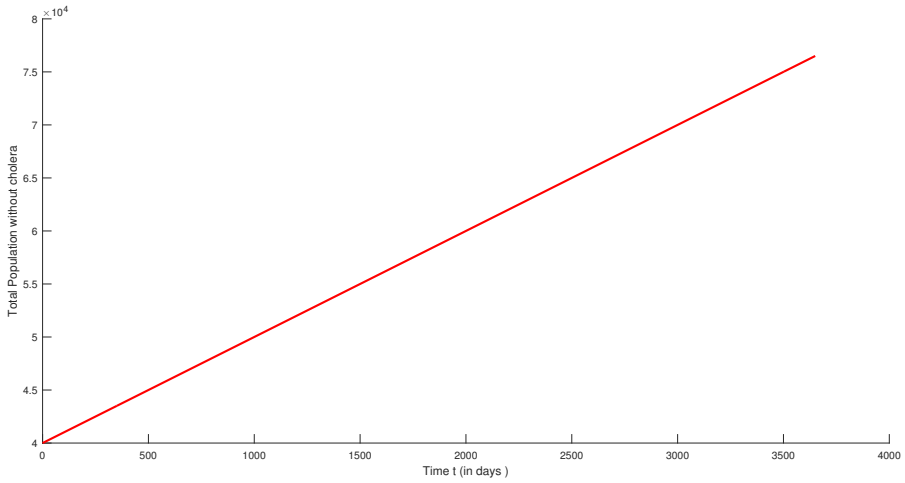

Figure 11. *Total population in absence of cholera disease.*

In figure 13: Show the total population of individuals in presence of cholera. During cholera outbreak the total population decreases as the individuals get infected and move to infected class and others die out until a stable point is reached. If cholera is not controlled the population may decrease further as cholera have been known to wipe out a whole community.

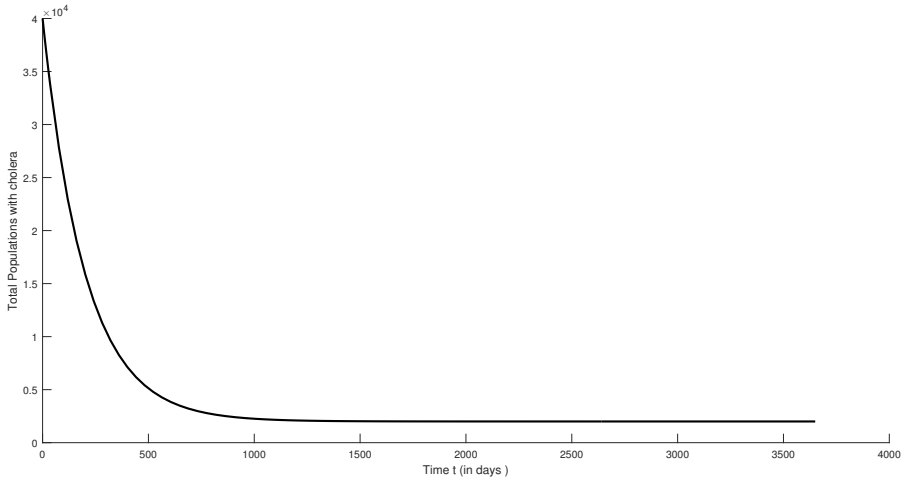

Figure 12. *Total population in presence of cholera disease.*

3.7. The impact of cholera, induced achlorhydria condition with treatment as an intervention.

Figure 14: Show a sharp decrease in total population this is due to cholera disease and also implication of the induced achlorhydria condition which help to fuels cholera until a stable point is reached. The impact of cholera in figure 14 is much greater than that for figure 13 since achlorhydria increase cholera prevalence.

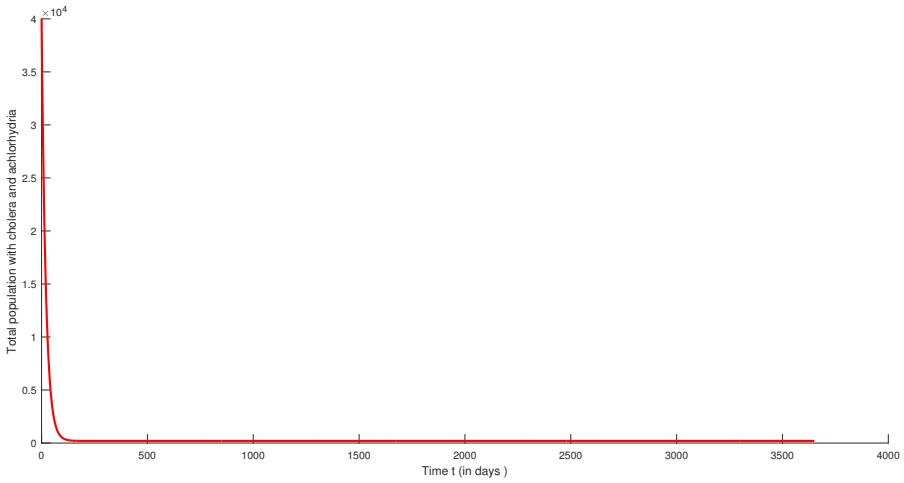

Figure 13. *Total population in presence of cholera and achlorhydria condition.*

Figure 15: Show treatment as a control strategy applied on total cholera infective population, treatment significantly reduces cholera transmission and mortality rate due to cholera. During cholera outbreak treatment should be applied either through medication or oral re-hydration.

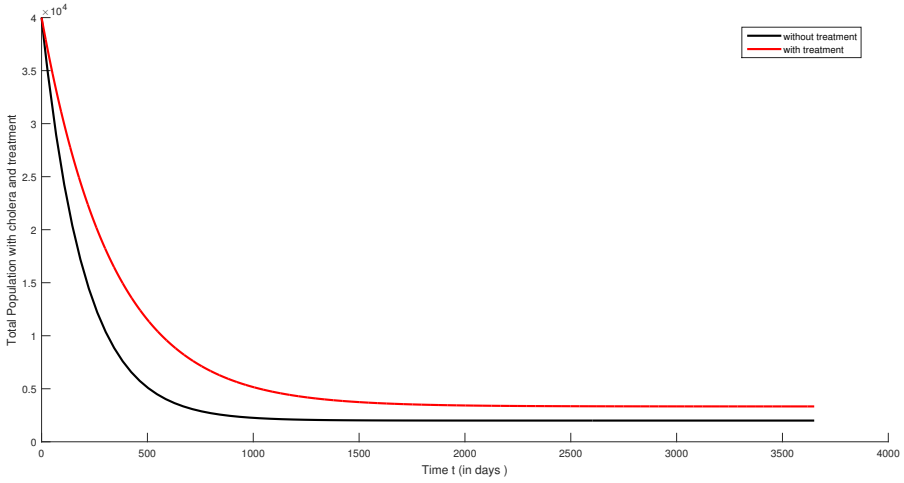

Figure 14. *Total population in presence and treatment as control.*

Figure 16: Show treatment as a control strategy applied on cholera infective with induced achlorhydria condition population and its effect, this class is hardly hit by cholera as cholera is fueled better by this condition. Applying treatment as control strategy will have significant effect through reducing transmission and mortality rate.

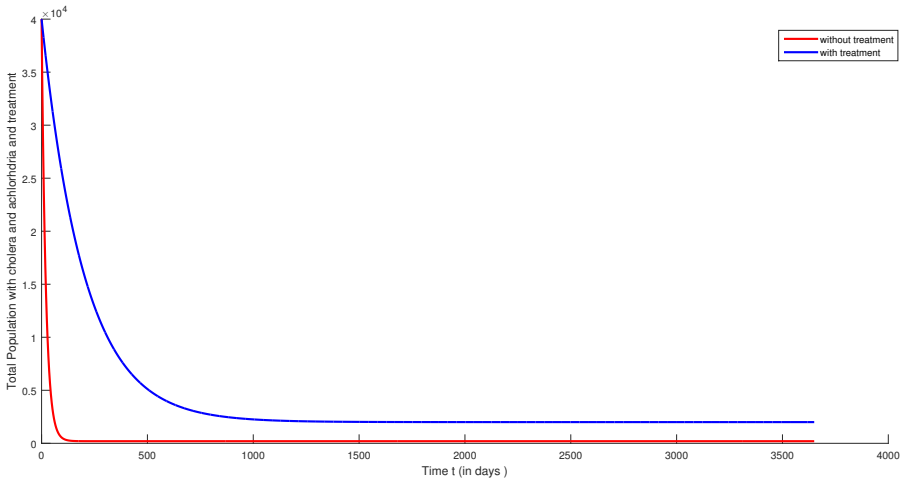

Figure 15. *Total population in presence of cholera and achlorhydria condition.*

3.8. Conclusion

In this paper, we formulated a mathematical model for cholera incorporating the dynamic of the induced achlorhydria condition and treatment. We studied the stability of the disease free and endemic equilibrium point. The results of the disease free equilibrium showed that the model is both locally and globally stable when $R_0 < 1$, thus, reducing R_0 to less than unity reduces the disease spread. Next we studied the endemic equilibrium which we found it to be asymptotically stable when $R_0 > 1$. Michaelis-menten equation in microbiology were used to show variation in hydrochloric acid concentration in the digestive system and how it affect the development of achlorhydria condition induced by *Vibrio cholerae*. Numerical analysis shows that in the presence of achlorhydria condition the disease propagate faster and if individuals with this condition are treated or correct mechanism is done by inducing development of enough hydrochloric acid first cholera disease can be eradicated with ease.

3.9. Conflict of interest

The authors declare that they have no financial and personal relationships with other people or organizations that can inappropriately influence their work. There is no professional or other personal interest of any nature or kind in any product, service or company that could be construed as influencing the position presented in or the review of the paper.

Acknowledgments

We are grateful to the administrative staff of the Department of Physical Sciences at Chuka University for their hospitality and assistance with research-related matters.

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