International Journal of Innovation and Applied Studies
ISSN 2028-9324 Vol. 19 No. 1 Jan. 2017, pp. 46-54

http://www.ijias.issr-journals.org/

MATHEMATICAL AND SENSITIVITY ANALYSIS OF THE DYNAMICAL SPREAD OF CHOLERA

S. O. Adewale[1], G. A. Adeniran[1], I. A. Olopade[2], S.O. Ajao[1], and I. T. Mohammed[3]

[1]Department of Pure and Applied Mathematics, P.M.B. 4000, Ladoke Akintola University of Technology (LAUTECH), Ogbomoso, Oyo State, Nigeria

[2]Department of Mathematics and Computer Science, P.M.B. 002, Elizade University, Ilara-Mokin, Ondo State, Nigeria

[3]Department of Statistics, Osun State Polytechnic, P.M.B. 301, Iree, Osun State, Nigeria

ABSTRACT: Sensitivity analysis was performed on the mathematical model of Cholera to determine the influence and importance of each parameter on the basic reproduction number (R_0) in the dynamical spread of Cholera. Basic Reproduction Number (R_0) was obtained using next generation matrix method (NGM). The disease free equilibrium was analyzed for stability and the analysis shows that the disease free equilibrium point is globally asymptotically stable whenever the basic reproduction number is less than unity i.e ($R_0<1$). Also, there exist endemic equilibrium points of the model whenever $R_0>1$. The relative sensitivity indices of the model with respect to each parameter in the basic reproduction number is calculated in order to find the most sensitive parameter which the medical practitioners and policy health makers should work on in order to reduce the spread of cholera in the society. The result shows that effective contact rate and fraction of individuals with low immunity are the most sensitive parameters in the reproduction number.
Numerical simulation was carried out by MAPLE 17 software using Runge-kutta method of order four to show the effects of contact rate and fraction of individuals with low immunity in the dynamical spread of Cholera. This work will allow the health policy makers to know the best control measure to be adopted in order to have disease free environment.

KEYWORDS: Cholera, Reproduction Number, Critical Point, Sensitivity analysis, Stability.

1 INTRODUCTION

Cholera is a deadly disease that is majorly caused by the bacterium called *Vibrio Cholera*. It belongs to a class of water-borne disease which occurs as a result poor sanitation and dirty water. The cholera bacteria release a toxin which makes it difficult for the body system to absorb liquids and makes an infected person to become dehydrated. This dehydration can lead to loss of life within two or three hours if not given medical attention on time [10]. An estimate of 1.4 to 4.3 million cases occurs each year with the total death of 28000 to 142000 worldwide [14].

The bacteria transmission involve two stages which are human and environmental stages which means that cholera transmission could be from environment to human and person to person transmission. Its transmission is common in an area where is no good environmental sanitation and lack of food/personal hygiene which creates avenue for cholera spread. Majorly there are two means of cholera transmission which are water and sea foods that are contaminated by the bacteria [9, 2, 5].

The time frame from the point of exposure to the time of appearance of cholera symptoms (incubation period) ranges between the hours of two to five days. The infected person develops the following symptoms after infection which includes: watery diarrhea, vomiting, loss of skin elasticity, thirst and muscle cramps [3, 14, 15].

Cholera can be treated through the use of antibiotics and fluid replacement therapy as this will reduce the spread and the death due to cholera infection in the environment [15].

Corresponding Author: S. O. Adewale

Mathematical modeling has been an important tool in understanding the disease transmission dynamics and also in making decision as regards the intervention mechanisms for the control of disease. Sani et al. [12] worked on a deterministic mathematical model on cholera dynamics and some control strategies. In their study, a system of four differential equations with two control measures which are therapeutic treatment and sanitary measures were considered. Stephen and Nkuba [13] also worked on mathematical model for the dynamics of cholera with control measures. They formulated a mathematical model that captures some essential dynamics of cholera transmission with public health education campaigns, vaccination, sanitation and treatment as control strategies in limiting cholera disease. Madubueze et al. [8] aslo considered the bifurcation and stability analysis of the dynamics of cholera model with controls. The existence of backward bifurcation is investigated in their work and the numerical simulation performed revealed that combine control measures will help to reduce the spread of cholera in the human population. Pransenjit Das and Debasis Mukherjee [11] worked on the qualitative analysis of a cholera bacteriophage model. In their work, they concluded that by using phage as a biological control agent in endemic areas, one may also influence the temporal dynamics of cholera epidemic while reducing the excessive use of chemicals. Adewale et al. [1] worked on the mathematical analysis of the effect of growth rate of vibrio-cholera in the dynamical spread of cholera. In their work, they developed a mathematical model that incorporated phage virus which serves as a biological control of cholera bacteria in the population; they concluded that phage virus plays a vital role in reducing the spread of cholera in the population. Jing et al. [6] worked on the mathematical analysis of a cholera model with vaccination. In their work, they performed sensitivity analysis of the basic reproduction number on the parameters involved in order to determine the relative importance to disease transmission and showed that an imperfect vaccine is always beneficial in reducing disease spread within the community.

In this paper, we formulated a new five compartmental model for the spread of cholera in order to perform sensitivity analysis as to detect the parameters that influence the increase in basic reproduction number, since R_o is the average number of secondary infection generated by a single infected individual in his or her infectious period in the population of susceptible.

2 MATHEMATICAL MODEL FORMULATION

The population size at time t denoted by N(t) is sub-divided into five (5) compartments of Susceptible individual S(t), Exposed individual E(t), Infected individual $I(t)$, Recovered individual R(t) and Bacteria population B(t) so that

$$N(t) = S(t) + E(t) + I(t) + R(t) \tag{1}$$

The susceptible population is increased by the recruitment of people (either by birth or immigration) into the population, all recruited individuals are assumed to be susceptible at a rate π, the population of Susceptible is further increased by the population of individual that are recovered at the rate (ω).Finally, the susceptible population decreases by infection which can be acquired following effective contact with infectious individuals only at a rate λ given by

$$\lambda = \frac{\beta(E + \eta_1 I + \eta_2 B)}{N} \tag{2}$$

and also by natural death at the rate (μ). Hence,

$$\frac{dS}{dt} = \pi - \lambda S - \mu S + \omega R \tag{3}$$

A fraction ε_1 of newly infected individuals with low immunity move to the exposed class E, while the remaining fraction ($1-\varepsilon_1$) move to the infected class I. The population of exposed class is reduced by the natural death rate (μ) and the progression rate (κ). Hence,

$$\frac{dE}{dt} = \varepsilon_1 \lambda - (\kappa + \mu)E \tag{4}$$

The population of Infected Cholera individual is increased by the remaining fraction of low immunity individual at the rate (1-ε_1) and the progression of exposed cholera individual at the rate (κ). The population is decreased by the treatment of cholera infected individuals at the rate (τ_1), natural death of cholera infected individual at the rate (μ) and the disease induced death at the rate (δ). Hence,

$$\frac{dI}{dt} = (1-\varepsilon_1)\lambda S + \kappa E - (\tau_1 + \mu + \delta)I \quad (5)$$

The population of Recovered Cholera individual is increased by the number of infected individuals that are treated and recovered at the rate (τ_1). The population is decreased by the loss of immunity of an individual after being recovered from cholera at the rate (ω) and the natural death of recovered individual at the rate (μ). Hence,

$$\frac{dR}{dt} = \tau_1 I - (\omega + \mu)R \quad (6)$$

The population of cholera bacteria is increased by the growth of *Vibrio- cholera* at the rate g and the contribution of each infected individual with the cholera bacteria into *Vibrio- cholera* environment. The population is further reduced by the natural death of the bacteria at the rate (μ_b). Hence,

$$\frac{dB}{dt} = gB + \alpha I - \mu_b B \quad (7)$$

Thus in summary, the dynamics transmission model is given by the following system of non-linear differential equations.

$$\left.\begin{aligned} \frac{dS}{dt} &= \pi - \lambda S - \mu S + \omega R \\ \frac{dE}{dt} &= \varepsilon_1 \lambda S - (\kappa + \mu)E \\ \frac{dI}{dt} &= (1-\varepsilon_1)\lambda S - (\tau_1 + \mu + \delta)I + \kappa E \\ \frac{dR}{dt} &= \tau_1 I - (\omega + \mu)R \\ \frac{dB}{dt} &= gB + \alpha I - \mu_b B \end{aligned}\right\} \quad (8)$$

Table 1: Variables and Descriptions

Variables	Descriptions
S	Susceptible individuals
E	Exposed Individuals
I	Infected Individuals
R	Recovered Individuals
B	Bacteria Population

Table 2: Parameters and Descriptions

Parameters	Descriptions
π	Recruitment rate into Susceptible
ω	Recovery rate
ε_1	Fraction of individual with Low immunity
κ	Progression rate
τ_1	Treatment rate
δ	Disease induced death rate
G	Growth rate of bacteria
α	Contribution of each infected in aquatic environment
μ_b	Bacteria death rate
β	Effective contact rate
μ	Natural death rate
η_1	Modification parameter of Infected Individuals
η_2	Modification parameter of the Bacteria

3 ANALYSIS OF THE MODEL

Lemma1: The closed set $D=\{(S,E,I,R,B)\in R_+^5 : N\le \frac{\pi}{\mu}\}$ is positively-invariant and attracting with respect to model (8) above.

Proof: Consider the biologically-feasible region $D=\{(S,E,I,R,B)\in R_+^5 : N\le \frac{\pi}{\mu}\}$. We shall show that D is positive invariance (i.e all solutions in D for all time t>0). The rate of change of the total population obtained by adding all the equations D in model (8), is given

$$\frac{dN}{dt}=\pi-\mu N-\delta I \tag{9}$$

Therefore, $\frac{dN}{dt}$ <0, whenever the sub total population $N>\frac{\pi}{\mu}$. Note that $\frac{dN}{dt}$ is bounded by $\pi-\mu N$ and a standard comparison theorem [7] can be used to show that $N(t)\le N(0)e^{-\mu t}+\frac{\pi}{\mu}(1-e^{-\mu t})$ in particular, $N(t)\le\frac{\pi}{\mu}$ if, $N(0)\le\frac{\pi}{\mu}$. Therefore, all solution of the model with initial conditions in D remains there for t>0 (i.e the $\omega-$limits sets of the system (8) are contained in D). This implies that D is positively-invariant and attracting. In this region, the model can be considered as been epidemiologically and mathematically well- posed.

3.1 DISEASE FREE EQUILIBRIUM (DFE)

The DFE of the modeled equation (8) can be obtained by setting the right hand of the model to zero.

$$\varepsilon_0=(S_0,E_0,I_0,R_0,B_0)=(\frac{\pi_h}{\mu_h},0,0,0,0) \tag{10}$$

3.2 BASIC REPRODUCTION NUMBER (R_0)

The basic reproduction number R_0 measures the average number of secondary infected individual generated in his/her infectious period in the population of susceptible. It is an important tool that determines whether the disease will dies out or persists and become endemic. When $R_0<1$, the disease dies out and whenever $R_0>1$, the disease persists and become endemic. It is obtained by taking the largest dominant eigenvalue of

$$R_o=\left(\frac{\partial F(E_0)}{\partial x_j}\right)\left(\frac{\partial V(E_0)}{\partial x_j}\right)^{-1} \tag{11}$$

It is given by $R_0=\rho(FV^{-1})$ where F is the new infection transfer terms; V is the non-singular matrix of the remaining transfer terms and ρ is the spectral radius.

The basic reproduction number R_0 of the model (8) is calculated using next generation matrix [3]. Then,

$$F=\begin{pmatrix} \varepsilon_1\beta & \varepsilon_1\eta_1\beta & 0 & \varepsilon_1\eta_2\beta \\ (1-\varepsilon_1)\beta & (1-\varepsilon_1)\eta_1\beta & 0 & (1-\varepsilon_1)\eta_2\beta \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{12}$$

$$V=\begin{pmatrix} k_1 & 0 & 0 & 0 \\ -\kappa & k_2 & 0 & 0 \\ 0 & -\tau_3 & k_3 & 0 \\ 0 & -\alpha & 0 & k_4 \end{pmatrix} \tag{13}$$

Where $k_1 = \kappa + \mu$, $k_2 = \tau_3 + \mu + \delta$, $k_3 = \omega + \mu$ and $k_4 = \mu_b - g$

The eigenvalue of FV^{-1} are

$$\begin{pmatrix} 0 \\ 0 \\ 0 \\ \dfrac{\beta(\alpha\eta_2\varepsilon_1\kappa - \alpha\eta_2 k_1\varepsilon_1 + \eta_1 k_4\kappa\varepsilon_1 - \eta_1 k_1 k_4\varepsilon_1 + \alpha\eta_2 k_1 + \eta_1 k_1 k_4 + k_2 k_4\varepsilon_1)}{k_1 k_2 k_4} \end{pmatrix} \tag{14}$$

Hence the basic reproduction number R_0 for the normalized model (8) is given by

$$R_0 = \frac{\beta(\alpha\eta_2\varepsilon_1\kappa - \alpha\eta_2 k_1\varepsilon_1 + \eta_1 k_4\kappa\varepsilon_1 - \eta_1 k_1 k_4\varepsilon_1 + \alpha\eta_2 k_1 + \eta_1 k_1 k_4 + k_2 k_4\varepsilon_1)}{k_1 k_2 k_4} \tag{15}$$

3.3 GLOBAL STABILITY OF THE MODEL

Here, the global asymptotic stability (GAS) property of the DFE of the Cholera model (8) will be explored.

Theorem 1: The disease free of the system (8) is globally stable whenever the $R_0 < 1$ and unstable if $R_0 > 1$.

Proof: it follows that $S = N^* - E - I - R$ at the steady state. The proof is based on using the comparism theorem [7] to prove the global stability.

Using comparison method, we have,

$$\begin{pmatrix} \dfrac{dE}{dt} \\ \dfrac{dI}{dt} \end{pmatrix} = (F - V)\begin{pmatrix} E \\ I \end{pmatrix} - F_i\begin{pmatrix} E \\ I \end{pmatrix}$$

Then,

$$\begin{pmatrix} \dfrac{dE}{dt} \\ \dfrac{dI}{dt} \end{pmatrix} = (F - V)\begin{pmatrix} E \\ I \end{pmatrix}$$

According to Driesssche and Watmough [4], all the eigen values of the matrix F – V have negative real parts. It follows that the linearized differential inequality system above is stable whenever $R_o < 1$. Consequently, by comparison theorem [7]. We have that $E = I = R = B = 0, \rightarrow (0,0,0,0)$ as t $\rightarrow \infty$. Substituting $E = I = R = B = 0,$ into (8), we have that $S(t) \rightarrow S(0)$ as $t \rightarrow \infty$. Hence, we have a positive invariant region. It follows that disease free equilibrium is globally asymptotically stable whenever $R_0 < 1$.

3.4 ENDEMIC EQUILIBRIUM

In this section, the possible existence of endemic (positive equilibra of the modeled equation (8) where at least one of the components of the model is non-zero) will be considered.

Let $\varepsilon_1^{**} = (S^{**}, E^{**}, I^{**}, R^{**}, B^{**})$ represents any arbitrary endemic equilibrium of the model equation.

Solving the equations of the system at steady-state gives

$$E^{**} = \frac{\varepsilon_1 \lambda^{**} S_h^{**}}{k_1} = P_1 \lambda^{**} S_h^{**} \tag{16}$$

$$I^{**} = \frac{(1-\varepsilon_1)\lambda^{**}S^{**}}{k_2} + \frac{\kappa\varepsilon_1\lambda^{**}S_h^{**}}{k_1k_2} = P_2\lambda^{**}S_h^{**} \quad (17)$$

$$R^{**} = \frac{\tau_1}{k_3}\{\frac{(1-\varepsilon_1)}{k_2} + \frac{\kappa\varepsilon_2}{k_1k_2}\}\lambda^{**}S^{**} = P_3\lambda^{**}S^{**} \quad (18)$$

$$B^{**} = \frac{\alpha}{k_4}\{\frac{(1-\varepsilon_1)}{k_2} + \frac{\kappa\varepsilon_1}{k_1k_2}\}\lambda^{**}S^{**} = P_4\lambda^{**}S^{**} \quad (19)$$

Where $\lambda^{**} = \frac{\beta_C(E^{**} + \eta_1 I^{**} + \eta_2 B^{**})}{N^{**}}$ (20)

$$N^{**} = S^{**} + E^{**} + I^{**} + R^{**} + B^{**}$$

Where

$$P_1 = \frac{\varepsilon_1}{k_1}$$

$$P_2 = \frac{1-\varepsilon_1}{k_2} + \frac{\kappa\varepsilon_1}{k_1k_2}$$

$$P_3 = \frac{\tau_1}{k_3}\{\frac{(1-\varepsilon_1)}{k_2} + \frac{\kappa\varepsilon_1}{k_1k_2}\}$$

$$P_4 = \frac{\alpha}{k_4}\{\frac{(1-\varepsilon_1)}{k_2} + \frac{\kappa\varepsilon_1}{k_1k_2}\}$$

Substituting the expression in (16-19) into (20), we have

$$\lambda^{**}[S^{**} + P_1\lambda^{**}S^{**} + P_2\lambda^{**}S^{**} + P_3\lambda^{**}S^{**} + P_4\lambda^{**}S^{**}] = \beta_C[P_1\lambda^{**}S^{**} + \eta_1P_2\lambda^{**}S^{**} + \eta_2P_4\lambda^{**}S^{**}] \quad (21)$$

Dividing each term in (21) by $\lambda^{**}S^{**}$

we have $1 + P_1\lambda^{**} + P_2\lambda^{**} + P_3\lambda^{**} + P_4\lambda^{**} = \beta_C[P_1 + \eta_1P_2 + \eta_2P_4]$

$1 + P_5\lambda^{**} = \beta_C[P_1 + \eta_1P_2 + \eta_2P_4]$

Where $P_5 = P_1 + P_2 + P_3 + P_4 \geq 0$

$$1 + P_5\lambda^{**} = \beta_C[\frac{\varepsilon_1}{k_1} + \frac{\eta_1\tau_1}{k_2}\{\frac{(1-\varepsilon_1)}{k_2} + \frac{\kappa\varepsilon_1}{k_1k_2}\} + \frac{\eta_2\alpha}{k_4}\{\frac{(1-\varepsilon_1)}{k_2} + \frac{\kappa\varepsilon_1}{k_1k_2}\}] = R_0$$

Where,

Therefore, $1 + P_5\lambda^{**} = R_0$

$\lambda^{**} = \frac{R_0 - 1}{P_5} > 0$, Whenever $R_0 > 1$.

Therefore, there exists an endemic equilibrium Whenever $R_0 > 1$.

3.5 CHOLERA SENSITIVITY ANALYSIS

It is necessary to determine how sensitive the threshold quantity basic reproduction number is with respect to its parameters, this will help to understand which of the parameters causes reduction in R_O and parameters that increases R_O and these parameters must give attention in order to have most effective control of the disease. This analysis will help to know how important each parameter is to disease transmission. We compute the normalized forward sensitivity index of the reproduction number with respect to its parameters.

Definition: If a variable 'c' depends differentiably on parameter 'w', then, the normalized forward sensitivity index of 'c' with respect to 'w' is denoted by $X_C = \frac{c}{w}\frac{\partial w}{\partial c}$

As we have explicit formula for R_O as

$$X_C = \frac{dR_0}{dw} \times \frac{w}{R_0} \tag{22}$$

Sensitivity analysis of each parameter involved in R_0 is therefore calculated and show in the table below.

Table 3: Values of Numerical Sensitivity of Cholera

Parameters	Sensitivity Values
μ	-0.038733
ω	0.000000
ε_1	0.993541
κ	0.955328
τ_1	-0.001980
δ	-0.003959
G	-0.007821
α	0.000000
μ_b	0.007821
β	0.999910
η_1	0.006335
η_2	0.007038

4 NUMERICAL SIMULATION

In order to verify the effect of contact rate and low Immunity rate in the dynamical spread of Cholera, the following set of parameters were used $\pi = 2000$, $\beta_C = 0.2$, $\varepsilon_1 = 0.5$, $\mu_h = 0.02$, $\kappa = 0.5$, $\delta_C = 0.02$, $\tau_1 = 0.1$, $\eta_1 = 0.02$, $\eta_2 = 0.02$, $\mu_b = 0.001$, g=0.01, $\omega = 0.15$, $\alpha = 0.0001$.

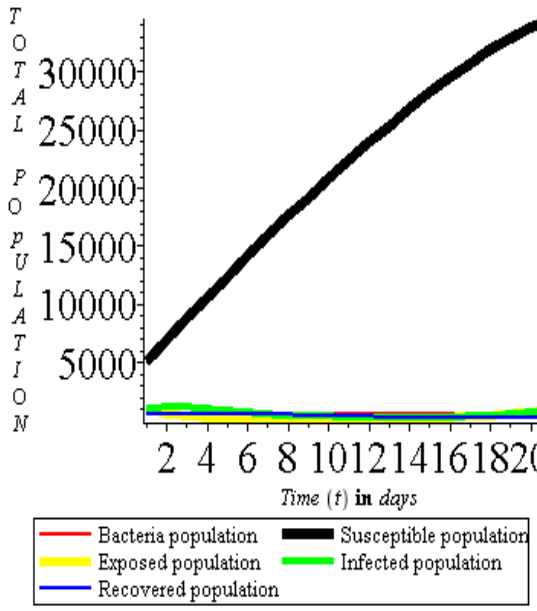

Figure 1: For the value of $\beta = 0.20$

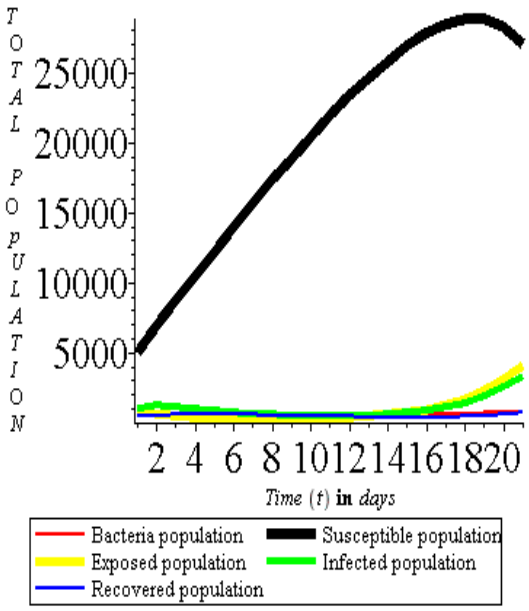

Figure 2: For the value of $\beta = 0.25$

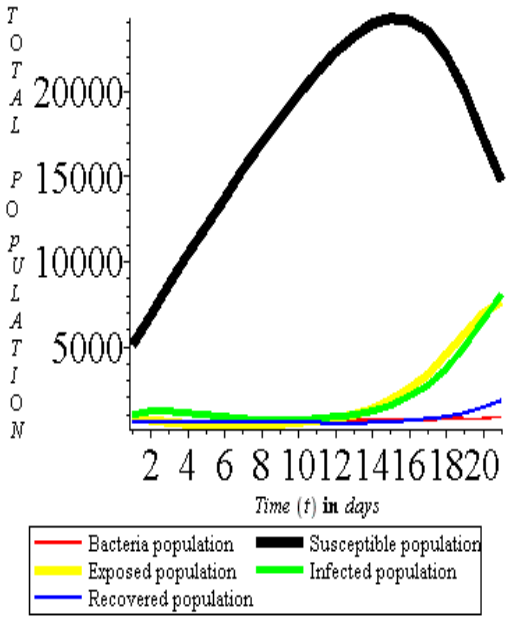

Figure 3: For the value of $\beta = 0.30$

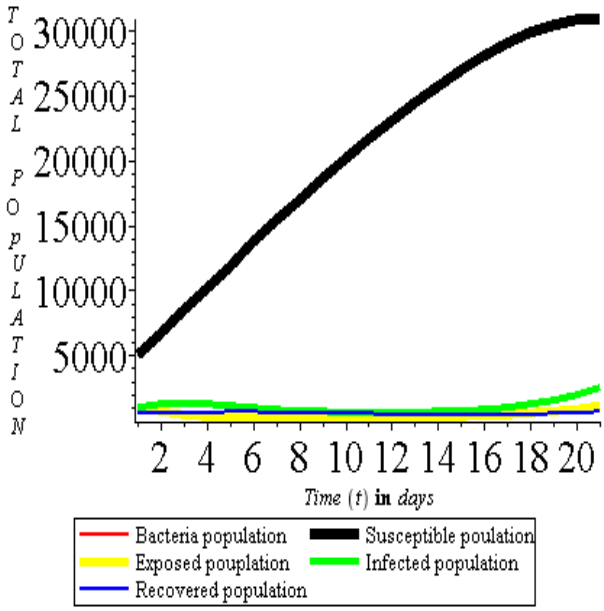

Figure 4: For the value of $\varepsilon_1 = 0.50$

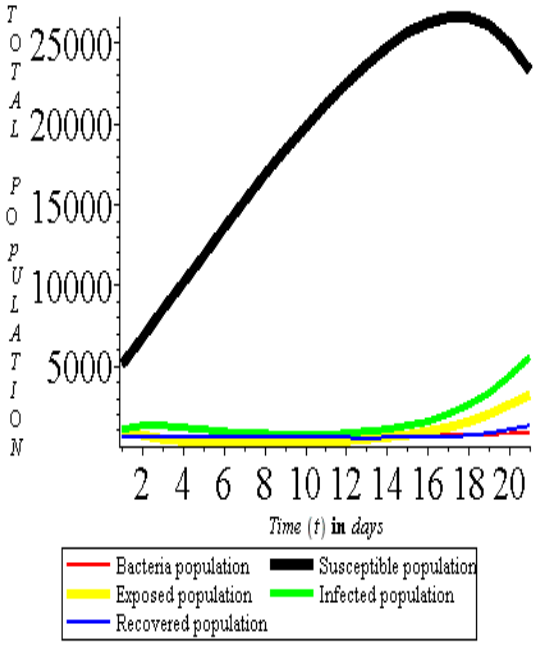

Figure 5: For the value of $\varepsilon_1 = 0.60$

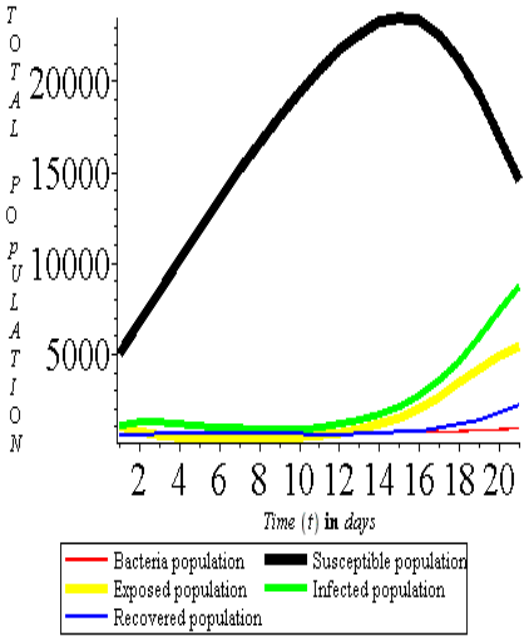

Figure 6: For the value of $\varepsilon_1 = 0.70$

5 Discussion And Conclusion

In this work, five (5) non-linear compartmental models was presented and analyzed to gain insight on the parameters that influence the outbreak of cholera in the community. Sensitivity analysis and numerical simulations of the model were carried out to determine the effects of parameters on the outbreak of Cholera disease. In figures **1-3** above, the effect of contact rate in the human population is considered and it was observed that as the contact rate increases in the human population, the susceptible population decreases while the exposed and infected population increases. Also figures **4-6** shows the effect of low immunity rate in an individual which reduces the susceptible population. As the immunity in an individual decreases, it makes the infected individual in the population to increase.

From our result, it was observed that the effective contact rate and the low immunity rate were the key parameters that influenced the dynamical spread of Cholera in the community. In conclusion, efforts should be put in place by health policy makers to reduce the rate at which an individual come in contact with the cholera bacteria (*Vibrio Cholera*) and also work on the immunity of an individual in order to have disease free environment.

REFERENCES

[1] Adewale S.O., Adeniran G.A., Olopade I.A and Mohammed I.T. (2015): Mathematical analysis of the effect of growth rate of vibrio-cholera in the dynamical spread of cholera. Research journali's Journal of Mathematics volume 2, No. 3 page 1-18.

[2] Colwell R.R. and Hug A. (1994): Environmental Reservoir of Vibrio cholera the causative agent of cholera. Ann. N.Y Acad. Sci., 740, 44-53.

[3] CDC 2014: Cholera: General information. Available at www.cdc.gov/cholera/general/ accessed on 30/09/2061.

[4] Driessche P, and Watmough J. (2002): Reproduction numbers and sub-threshold endemic equilibrium for compartmental models of disease transmission, Mathematical Biosciences 180, 29-48.

[5] Hartley D.M., Morris,Jr J.G. and Smith D.L. (2006): Hyper infectivity a critical element in the ability of Vibrio cholera to cause epidemic. PLos Med., 3(1), 63-69.

[6] Jing an C., Zhanmin W. and Xueyong Z. (2014): Mathematical analysis of a cholera model with vaccination. Journal of Applied Mathematics Volume 2014, Article ID 324767, 16 pages. http://dx.doi.org/10.1155/2014/324767.

[7] Lakshmkanthan V., Leela S. and Martynyut A.A. (1989): Stability analysis of Non-Linear System. Marcel Dekker, Inc., New York and Basel.

[8] Madubueze C.E., Madubueze S.C. and Ajama S. (2015): Bifurcation and Stability Analysis of the Dynamics of cholera model with controls. International Journal of Mathematical, Computational, Physical, Electrical and Computer Engineering Vol 9, No 11, 2015.

[9] Nelson E.J., Chowdhuy A., Flynn J., Schild S., Bourassa L. et al. (2008): Transmission of Vibrio Cholera antagonized by lytic phage and entry into the aquatic environment. PLos pathogens 4(10), 1-15.

[10] Ochoche J.M. (2013): A mathematical model for the transmission dynamics of cholera with control strategy. International Journal of Science and Technology Volume 2, No. 11, November 2013.

[11] Prasenjit Das and Debasis Mukherjee (2012): ISRN Biomathematics Volume 2012(2012). Article ID 621939, 13 pages. http://dx.doi.org/10,5402/2012621939.

[12] Sani A.F., Ibrahim M.O. and Danbaba A. (2013): Deterministic Mathematics model of cholera predicting chances of its outbreak. International Journal of Scientific and Technology Research volume 2, Issue 4.

[13] Stephen E. and Nkuba N. (2015): A mathematical model for the dynamics of cholera with control measures. Applied and computational Mathematics. Vol, 4 No. 2, 2015, pp. 53-63. Doi: 10.11648/j.acm.20150402.14

[14] World Health Organization (2015), Cholera media Centre,
Fact Sheets available on www.who.int/mediacentre/factsheets/fs107/en/ (Accessed on 30/09/2016)

[15] Zukerman J.N., Rombo L. and Fish A. (2007): The burden risk of cholera: Implications for prevention and control. Lancet infect. Dis., 7(8), 521-530.