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MATHEMATICAL MODELLING AND ANALYSIS OF CHOLERA DISEASE DYNAMICS WITH CONTROL

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ABSTRACT
A deterministic mathematical model of cholera infection incorporating health education campaign, vaccination of susceptible humans, treatment of infected human and water sanitation is developed. It is shown that the solution of the model uniquely exist, it is positive and bounded in a certain region. The disease-free equilibrium (DFE) state of the model was determined and used to compute the basic reproduction number R_0, as a threshold for effective disease management. The result from stability analysis for the disease-free equilibrium state (DFEs) shows that it is locally as well as globally asymptotically stable whenever the basic reproduction number R_0, is less than unity ($R_0 < 1$). The results obtained from the sensitivity index of R_0 show that the control parameters of public health education campaign, vaccination of susceptible individuals, treatment of infected humans and water sanitation are crucial parameters to cholera management. Numerical simulations show that, expanded and improved vaccination among other interventions is crucial in decreasing cholera burden. Furthermore, from the numerical simulations and results it is recommended that a combination of mass and consistent public health education campaigns, expanded vaccination coverage, prompt treatment of infected individuals, with water sanitation, is vital to public health strategies in eradicating cholera infection and deaths in the shortest possible time.

Keywords: cholera, pathogen, reproduction number, stability, sensitivity

INTRODUCTION

Cholera is an acute diarrheal infection of the small intestine caused by a highly pathogenic gram-negative bacterium, Vibrio Cholerae. It is contracted through ingestion of food or water contaminated with vibrio cholerae, and untreated individuals suffer severely from profuse watery diarrhea and vomiting. The infection can cause a rapid dehydration and electrolyte imbalance and can lead to death (Azman, 2013, Ali et al., 2015; World Health Organisation, 2019).

Cholera transmission is closely linked to inadequate access to clean water and sanitation facilities. Typical at-risk areas include peri-urban slums, and camps for internally displaced persons or refugees, where minimum requirements of clean water and sanitation are not being met. The dynamics of cholera involve multiple interactions between the human host, the pathogen, and the environment which constitute to both direct human-to-human and indirect environment-to-human transmission pathways (WHO,2019).

The number of cholera reported cases has continued to be high over the last few years with countries like Zimbabwe, Vietnam, Nigeria, Haiti and Zambia experiencing different cholera outbreaks (Chirambo et al., 2016, WHO, 2019). In 2017, 34 countries were reportedly affected by cholera, of this number of countries, 9 [Yemen (over 1 million case}, Democratic Republic of Congo, Ethiopia, Haiti, Nigeria (Borno most especially), Somalia, South Sudan and Zambia (Lusaka)] faced very severe outbreaks. The outbreaks led to the infection of approximately 1,227,391 people, from which 5,654 deaths were recorded (179,835 cases 3220 deaths from 14 African countries and 13,818 cases and 169 deaths from Americas: (Haiti alone recorded 13,681 cases (Legros, 2019).

Cholera, according to Tarh (2019) is still a problem in the world today. A huge population of deaths due to cholera disease still occur in Sub-Sharan Africa (Nigeria most especially), Asia, the Americas and other developing countries, where approximately 1.7 billion inhabitants of these areas are still served by faecally polluted water sources, while 2.4 billion, lack the majorly required sanitary conditions of living (Shrivastava et al., 2019). This is a clear indication that cholera is still a major global public health challenge.

Due to its huge impact on public health, and social and economic development, cholera has been the subject of extensive studies in clinical, experimental and theoretical fields (Mukandavire et al., 2011).

Mathematical modeling is an important tool used in analyzing the dynamics of infectious disease. Several models have been

formulated and analysed to explain the dynamics of cholera transmission.

Codeço (2001) proposed a deterministic model which, explicitly incorporated the role of the environment, i.e. Vibrio Cholerae concentration in the aquatic reservoir, into a regular SIR system to form a combination of human-environment $(SIR - B)$ epidemiological model.

Hartley et al, (2006) modified Codeco (2001)'s model to consist of a hyper infectious state of the pathogen based on laboratory observations.

Mukandavire et al., (2011) simplified the model by Hartley et al., (2006) to study the 2008 – 2009 cholera outbreaks in Zimbabwe. Their model explicitly considered both "fast" human-to-human and "slow" environment-to-human transmission pathways. The results demonstrated that both modes of transmission contributed in sustaining cholera in Zimbabwe.

Falaye et al., (2018) modified the cholera model proposed by Mukandavire et al., (2011) by incorporating three containment options such as vaccination, therapeutic treatment and water treatment but did not incorporate the role of public health education control strategy in their model.

Education which is a key tool in disease-control, is often overlooked (Hargreaves et al., 2008). It requires investment in people rather than biomedical interactions, but has the potential to lead to enormous benefits for relatively low cost. Cholera – specific education includes advising people with symptoms to seek medical care promptly, and improving sanitation and hygienic practices (Einarsd'ottir and Gunnlaugssion, 2001). Thus it is instructive to carry out modeling studies that focus on non-biochemical intervention such as public health education.

Therefore our objective is to modify the model by Falaye et al., (2018) by adding public health education parameter as a control strategy. So we have four types of controls: public health education campaign, vaccination, therapeutic treatment and water sanitation. We are able to rigorously analyse both the stability and sensitivity of the corresponding autonomous dynamic system. We will then use numerical simulation to explore various controls – both single and multiple control strategies.

The rest of this paper is structured as follows. The model is designed in Section 2. The local and global asymptotic stability property of the model is investigated in Section 3. Sensitivity analysis of the basic reproduction number with respect to the model parameters is analysed in Section 4. The numerical simulation is carried out in Section 5 while Section 6 deals with discussion of results and concluding remarks in Section 7.

MODEL FORMULATION

We begin our model formulation by introducing the model by Falaye et al., (2018).

Basic Assumptions of the model by Falaye et al., (2018)

The following are the assumptions of the existing model by Falaye et al., (2018):

(a) Introduction of vaccination to the susceptible at the rate q.
(b) Applying therapeutic treatment to the infected at the rate of u.
(c) Water sanitation leading to the death of vibrios (V. cholera) at the rate z.

The variables and parameters used in the existing model are defined in Table 1.

Table 1: Variables and Parameters used in the model and their description

Variable/Parameter	Description
$S(t)$	The number of susceptible hosts at time t
$I(t)$	The number of infectious human hosts at time t
$B(t)$	The vibrio concentration in contaminated water at time t
$R(t)$	The number of recovered human hosts at time t
ρ	Recruitment rate
α	Rate of injecting V. Cholerae from contaminated sources
K	Concentration of Vibrio Cholerae in food and water that yield 50% chance of catching cholera disease.
β	human –to- human transmission rate
ψ	Human death rate
q	Vaccination rate
σ	Recovery rate of infected human
δ	Disease induced death rate

u	Treatment rate
ε	The rate of shedding of V.Cholerae by humans through untreated wastes
ϕ	Natural death rate of V.Cholerae
z	Water sanitation rate

The Equations of the existing Model

Using the above assumptions, variables and parameters, Falaye et al., (2018) derived the following model equations.

$$\frac{dS}{dt} = \rho - \alpha\frac{B}{K+B}S - \beta SI - (\psi + q)S \quad (1)$$

$$\frac{dI}{dt} = \alpha\frac{B}{K+B}S + \beta SI - (\sigma + \delta + \psi + u)I \quad (2)$$

$$\frac{dB}{dt} = \varepsilon I - (\phi + z)B \quad (3)$$

$$\frac{dR}{dt} = (\sigma + u)I + qS - \psi R \quad (4)$$

With the non-negative initial conditions

$$S(0) \geq 0, I(0) \geq 0, B(0) \geq 0, R(0) \geq 0 \quad (5)$$

BASIC ASSUMPTION OF THE MODIFIED MODEL

Here, we modify the cholera model proposed in Falaye et al., (2018)'s work by incorporating:

(i) The role of public health education campaign at the rate of γ in our model.

From the above assumptions, definition of variables and parameters, the interactions and flow in the different compartments are as depicted in the schematic flow diagram below.

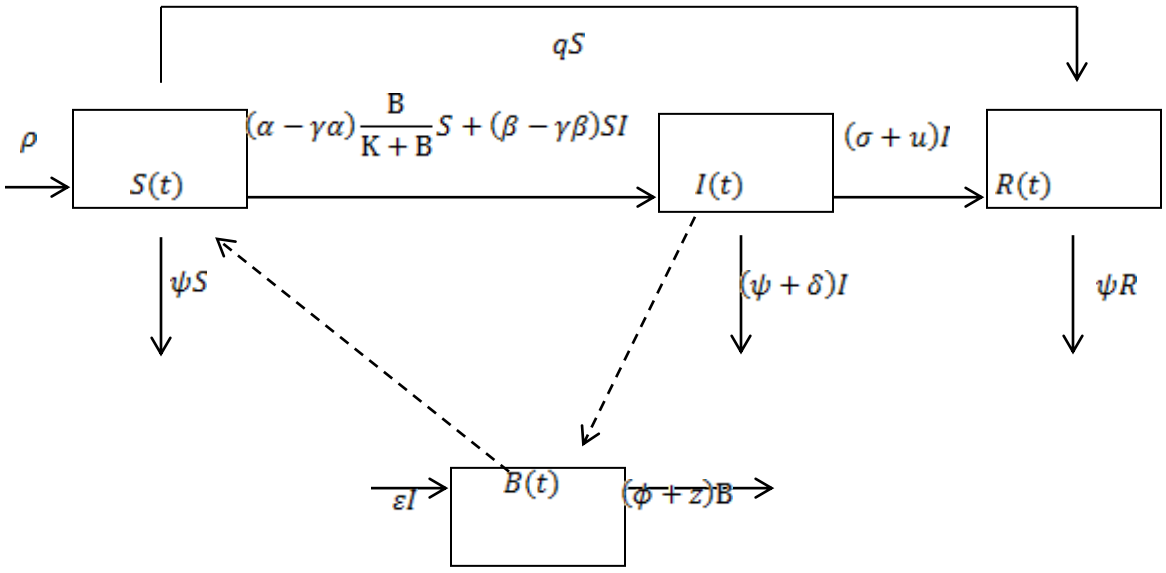

Figure 1: Schematic description of the mathematical model

Susceptible, Infected, Pathogen and Recovered Population

The population of susceptible humans S, are recruited at the rate ρ. It is reduced by infection contracted by the susceptible individuals either by ingesting vibrios from contaminated sources at a rate, $\frac{B}{K+B}$, or through human-to-human transmission at a

rate β. The susceptible population is further reduced by natural death at the rate ψ and after being vaccinated at the rate q. Putting all these definitions together leads to the following expression for the rate of change of the susceptible population.

$$\frac{dS}{dt} = \rho - (\alpha - \gamma\alpha)\frac{B}{K+B}S - (\beta - \gamma\beta)SI - (\psi + q)S$$

Infectious humans I are generated as a result of infection contracted by the susceptible individuals either by ingesting vibrios from contaminated sources at a rate $\frac{B}{K+B}$, or through human-to-human transmission at a rate β. It is diminished by recovery from cholera infection at the rate σ, treatment at the rate u, disease-induced death at the rate δ and natural death at the rate ψ, so that

$$\frac{dI}{dt} = (\alpha - \gamma\alpha)\frac{B}{K+B}S + (\beta - \gamma\beta)SI - (\sigma + \delta + \psi + u)I$$

The pathogen population, B that is the vibrio concentration in contaminated water is increased through infectious individuals shedding vibrios cholerae at the rate ε. It is diminished by sanitation at the rate, z, and natural death at the rate ϕ, so that

$$\frac{dB}{dt} = \varepsilon I - (\phi + z)B$$

The population of recovered humans R are generated through vaccination of susceptible individuals at the rate, q, recovery from cholera infection at the rate σ, treatment at the rate u It is reduced by natural death at the rate ψ. Thus,

$$\frac{dR}{dt} = (\sigma + u)I + qS - \psi R$$

MODEL EQUATIONS

The above assumptions and formulations lead to the following system of ordinary differential equations:

$$\frac{dS}{dt} = \rho - (\alpha - \gamma\alpha)\frac{B}{K+B}S - (\beta - \gamma\beta)SI - (\psi + q)S \quad (6)$$

$$\frac{dI}{dt} = (\alpha - \gamma\alpha)\frac{B}{K+B}S + (\beta - \gamma\beta)SI - (\sigma + \delta + \psi + u)I \quad (7)$$

$$\frac{dB}{dt} = \varepsilon I - (\phi + z)B \quad (8)$$

$$\frac{dR}{dt} = (\sigma + u)I + qS - \psi R \quad (9)$$

With the non-negative initial conditions

$$S(0) \geq 0, I(0) \geq 0, B(0) \geq 0, R(0) \geq 0 \quad (10)$$

Basic Properties of the Model Equations

All model variables and parameters are assumed to be non-negatives for all $t \geq 0$ since the model monitors changes in the population.

Existence of Solution

Let $X: \mathbb{R} \to \mathbb{R}^4$

$$t \to (S(t), I(t), B(t), R(t))$$

and

$$F: \mathbb{R}^4 \to \mathbb{R}^4$$

$$X(t) \to F(X(t)) = \left(\frac{dS(t)}{dt}, \frac{dI(t)}{dt}, \frac{dB(t)}{dt}, \frac{dR(t)}{dt}\right)$$

Then the system (1) – (4) becomes

$$X(t) = F(X(t)), X(0) = X_0$$

Theorem 1. (Existence and uniqueness) The model (6) – (9) is continuous and satisfies the Cauchy-Lipschitz condition (Grinshaw, 1990).

Proof:
From equation (6)

$$\mathrm{G(t,S)} = \frac{dS}{dt} = \rho - (\alpha - \gamma\alpha)\frac{\mathrm{B}}{\mathrm{K+B}}S - (\beta - \gamma\beta)SI - \psi S - qS \tag{11}$$

Then

$$\frac{\partial G(t,S)}{\partial S} = -(\alpha - \gamma\alpha)\frac{\mathrm{B}}{\mathrm{K+B}} - (\beta - \gamma\beta)I - \psi - q \tag{12}$$

We have that the function $\mathrm{G(t,s)}$ and its partial derivative $\frac{\partial G(t,S)}{\partial S}$ are defined and continuous at all points $\mathrm{(t,S)}$.

Similarly from equation (7)

$$\mathrm{G(t,I)} = \frac{dI}{dt} = (\alpha - \gamma\alpha)\frac{\mathrm{B}}{\mathrm{K+B}}S + (\beta - \gamma\beta)SI - \sigma I - \delta I - \psi I - uI \tag{13}$$

Then

$$\frac{\partial G(t,I)}{\partial I} = (\beta - \gamma\beta)S - \sigma - \delta - \psi - u. \tag{14}$$

We have that the function $\mathrm{G(t,I)}$ and its partial derivative $\frac{\partial G(t,I)}{\partial I}$ are defined and continuous at all points $\mathrm{(t,I)}$.

From equation (8)

$$\mathrm{G(t,B)} = \frac{dB}{dt} = \varepsilon I - \phi\mathrm{B} - z\mathrm{B} \tag{15}$$

Then

$$\frac{\partial G(t,B)}{\partial B} = -\phi - z \tag{16}$$

We have that the function $\mathrm{G(t,B)}$ and its partial derivative $\frac{\partial G(t,B)}{\partial B}$ are defined and continuous at all points $\mathrm{(t,B)}$.

And from equation (9)

$$\mathrm{G(t,R)} = \frac{\mathrm{dR}}{\mathrm{dt}} = (\sigma + u)I + qS - \psi R \tag{17}$$

Then

$$\frac{\partial G(t,R)}{\partial R} = -\psi \tag{18}$$

We have that the function $\mathrm{G(t,R)}$ and its partial derivative $\frac{\partial G(t,R)}{\partial R}$ are defined and continuous at all points $\mathrm{(t,R)}$.

Hence by the existence and uniqueness theorems, there exists a unique solution for $S(t), I(t), B(t), R(t)$ for all $\mathrm{t} \geq 0$.
We move to show that the solution satisfies the Lipschitz condition.
Using equation (11), we see that

$$\begin{aligned}
&|\mathrm{G(t,S_1)} - \mathrm{G(t,S_2)}| \\
&= \left|\left(\rho - (\alpha - \gamma\alpha)\frac{\mathrm{B}}{\mathrm{K+B}}S_1 - (\beta - \gamma\beta)S_1 I - (\psi + q)S_1\right)\right. \\
&\left. - \left(\rho - (\alpha - \gamma\alpha)\frac{\mathrm{B}}{\mathrm{K+B}}S_2 - (\beta - \gamma\beta)S_2 I - (\psi + q)S_2\right)\right| \\
&= \left|(-1)\left(\rho - (\alpha - \gamma\alpha)\frac{\mathrm{B}}{\mathrm{K+B}} + (\beta - \gamma\beta)I + (\psi + q)\right)(S_1 - S_2)\right| \\
&\leq \left((\alpha - \gamma\alpha)\frac{\mathrm{B}}{\mathrm{K+B}} + (\beta - \gamma\beta)I + (\psi + q)\right)|S_1 - S_2|
\end{aligned}$$

This implies that $|\mathrm{G(t,S_1)} - \mathrm{G(t,S_2)}| \leq M|S_1 - S_2|$ where $M = \left((\alpha - \gamma\alpha)\frac{\mathrm{B}}{\mathrm{K+B}} + (\beta - \gamma\beta)I + \psi + q\right)$ is a Lipschitz constant.
In a similar way, we obtained that the remaining variables satisfy the Lipschitz condition and thus, $\exists$ a unique solution $I(t), B(t), R(t) \forall\ t \geq 0$.

Theorem 2. (Positivity) Given the non-negative initial conditions (10), then the solutions $S(t), I(t), B(t)$ and $R(t)$ are non-negative $\forall\ t \geq 0.$

Proof:

From equation (6), we deduce that $\forall\ t \geq 0.$

$$\frac{dS}{dt} \geq -\left((\alpha - \gamma\alpha)\frac{B}{K+B} + (\beta - \gamma\beta)I + \psi + q\right)S$$

$$\frac{dS}{dt} \geq -\lambda S \tag{19}$$

Where $\lambda = (\alpha - \gamma\alpha)\frac{B}{K+B} + (\beta - \gamma\beta)I + \psi + q$

Integrating equation (19) gives

$$\ln|S| \geq \int -\lambda dt + C \ \Rightarrow |S| \geq Ce^{\int -\lambda dt} \Rightarrow S \geq S_0 e^{\int -\lambda dt}$$

Hence

$$S \geq S_0 e^{\int -\left((\alpha-\gamma\alpha)\frac{B}{K+B}+(\beta-\gamma\beta)I+\psi+q\right)} \geq 0 \tag{20}$$

where S_0 is the susceptible population at $t = 0$

The right hand side of (20) is always positive for $t \geq 0$

In the same way we show that I is positive for all $t \geq 0$

Using Birkhoff-Rota (1982)'s theorem, equation (7) can be solved for I as follows

$$\frac{dI}{dt} = (\alpha - \gamma\alpha)\frac{B}{K+B}S + (\beta - \gamma\beta)SI - (\sigma + \delta + \psi + u)I$$

$$\frac{dI}{dt} \geq -(\sigma + \delta + \psi + u)I$$

$$\int \frac{dI}{I} \geq -(\sigma + \delta + \psi + u)\int dt$$

$$\Rightarrow \ln I \geq -(\sigma + \delta + \psi + u)t + C$$

$$\Leftrightarrow I \geq I_0 e^{-(\sigma+\delta+\psi+u)t} > 0 \tag{21}$$

Here again, it is clear that the right hand side of the last inequality in (21) is always positive, hence I is positive for all $t \geq 0.$

Similarly, it follows that $B, R \geq 0.$

that is

$$\frac{dB}{dt} \geq -(\phi + z)B$$

Integrating with respect to B yields

$$B \geq B_0 e^{-(\phi+z)t} > 0 \tag{22}$$

And

$$\frac{dR}{dt} \geq -\psi R$$

$$\Leftrightarrow R \geq R_0 e^{-\psi t} > 0 \tag{23}$$

From the results in (18), (19), (20) and (21), we conclude that whenever $t \geq 0,$ the solutions of the systems (6) - (9) are positive.

We show in the following Theorem 3 that it is sufficient to consider the flow dynamics of the model (6) – (9) in a certain region $\Omega.$

Theorem 3. (Boundedness) All solution of $S(t), I(t), B(t), R(t)$ of the model (6) – (9) are bounded and remain in the region.

$$\Omega = \Omega_H \times \Omega_B \tag{24}$$

Where

$$\Omega_H = \left\{(S,I,R) \in \mathbb{R}_+^3 : 0 \leq (S(t)+I(t)+R(t)) \leq \frac{\rho}{\psi}\right\} \quad (25)$$

And

$$\Omega_B = \left\{B \leq \mathbb{R}_+ : 0 \leq B(t) \leq \frac{\varepsilon}{\phi+z}\right\} \quad (26)$$

Proof:

We begin by splitting the model (6) – (9) into human population $H(t) = S(t) + I(t) + R(t)$ and the bacteria population, $B(t)$. Then we have that

$$\frac{dH}{dt} = \rho - \psi(S+I+R) - \delta I$$
$$\leq \rho - \psi H$$

By integrating we obtain

$$H \leq \frac{\rho}{\psi} + Ce^{-\psi t}$$

Where C is a constant. Initially at $t = 0, H(0) - \frac{\rho}{\psi} \leq C$

Therefore

$$H \leq \frac{\rho}{\psi} + \left(H(0) - \frac{\rho}{\psi}\right)e^{-\psi t}$$

Thus

$$\lim_{t\to\infty} H \leq \frac{\rho}{\psi}$$

Similarly

$$\frac{dB}{dt} = \varepsilon I - (\phi+z)\mathrm{B} \leq \varepsilon - (\phi+z)\mathrm{B}$$

And

$$\lim_{t\to\infty} B \leq \frac{\varepsilon}{\phi+z}$$

This shows that the human and bacteria population are biologically feasible in the region (25) and (26) respectively. Therefore the solution of model (6) – (9) with the initial condition in (10) is bounded in the invariant region (24) $\forall\, t \geq 0.$

MODEL ANALYSIS

Since the equation (6) – (9) are independent of the variable R, it is suffice to consider the first three equations of system (6) – (9), our new system becomes

$$\frac{dS}{dt} = \rho - (\alpha - \gamma\alpha)\frac{\mathrm{B}}{\mathrm{K}+\mathrm{B}}S - (\beta - \gamma\beta)SI - (\psi+q)S \quad (27)$$

$$\frac{dI}{dt} = (\alpha - \gamma\alpha)\frac{\mathrm{B}}{\mathrm{K}+\mathrm{B}}S + (\beta - \gamma\beta)SI - (\sigma+\delta+\psi+u)I \quad (28)$$

$$\frac{dB}{dt} = \varepsilon I - (\phi+z)\mathrm{B} \quad (29)$$

Disease Free Equilibrium (DFE) State

The model (27) – (29) has a disease-free equilibrium (DFE) state by setting the right hand sides of equations (27) – (29) to zero and solving to obtain

$$\boldsymbol{E_0} = (S^*, I^*, B^*) = \left(\frac{\rho}{\psi+q}, 0, 0\right) \quad (30)$$

We will use the next generation operator method to compute the basic reproduction number R_0.

Basic Reproduction Number *R₀*

The basic reproduction number or reproductive number of an infectious disease is the average number of secondary infections when one infected individual is introduced into a host population where everyone is susceptible (Diekmann et al., 1990; Diekmann et al., 2010). We use the next generation matrix approach to compute the Basic Reproduction Number R_0.

The basic reproduction number *R₀* is the spectral radius of the product matrix FV^{-1}. That is, $R_0 = \tau(FV^{-1})$, (where τ denotes the spectral radius)

The associated non-negative matrix F, for the new infective terms and the non-singular M-matrix, V, for the remaining transfer terms at the DFE are respectively given by

$$F = \begin{pmatrix} \frac{\rho(\beta-\gamma\beta)}{\psi+q} & \frac{\rho(\alpha-\gamma\alpha)}{K(\psi+q)} \\ 0 & 0 \end{pmatrix} \tag{31}$$

and

$$V = \begin{pmatrix} (\sigma+\delta+\psi+u) & 0 \\ -\varepsilon & \phi+z \end{pmatrix} \tag{32}$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\sigma+\delta+\psi+u} & 0 \\ \frac{\varepsilon}{(\sigma+\delta+\psi+u)(\phi+z)} & \frac{1}{\phi+z} \end{pmatrix} \tag{33}$$

$$FV^{-1} = \begin{pmatrix} \frac{\rho(\beta-\gamma\beta)}{(\psi+q)(\sigma+\delta+\psi+u)} + \frac{\rho(\alpha-\gamma\alpha)\varepsilon}{K(\sigma+\delta+\psi+u)(\phi+z)(\psi+q)} & \frac{\rho(\alpha-\gamma\alpha)}{K(\psi+q)(\phi+z)} \\ 0 & 0 \end{pmatrix} \tag{34}$$

It follows that the basic reproduction number, denoted by R_0, is given by (where τ denotes the spectral radius)

$$R_0 = \frac{\rho(\beta-\gamma\beta)}{(\psi+q)(\sigma+\delta+\psi+u)} + \frac{\rho(\alpha-\gamma\alpha)\varepsilon}{K(\sigma+\delta+\psi+u)(\phi+z)(\psi+q)} \tag{35}$$

Local Stability of Disease Free Equilibrium (DFE) State

We investigate the local stability of the disease free (DFE) state by evaluating the associated Jacobian of equations (27) – (29) at the DFE state. The Jacobian matrix J for the system (27) – (29), evaluated at the disease-free equilibrium, $\mathbf{E_0}$ is given by

$$J(\mathbf{E_0}) = \begin{pmatrix} -(\psi+q) & -\frac{\rho(\beta-\gamma\beta)}{\psi+q} & -\frac{\rho(\alpha-\gamma\alpha)}{K(\psi+q)} \\ 0 & \frac{\rho(\beta-\gamma\beta)}{\psi+q} - (\sigma+\delta+\psi+u) & \frac{\rho(\alpha-\gamma\alpha)}{K(\psi+q)} \\ 0 & \varepsilon & -(\phi+z) \end{pmatrix} \tag{36}$$

Theorem 4: The DFEs of the model (27) – (29), given by $\mathbf{E_0}$, is locally asymptotically stable (LAS) if $R_0 < 1$ and $\mathbf{E_0}$ is unstable if $R_0 > 1$.

Proof:

It suffices to show that all the eigenvalues of the characteristic equation of the Jacobian matrix $J(\mathbf{E_0})$, have negative real parts.

The characteristic equation of the Jacobian matrix is given by

$$(-(\psi+q)-\lambda)\left[\left(-\left(\frac{(\sigma+\delta+\psi+u)(\psi+q)-\rho(\beta-\gamma\beta)}{\psi+q}\right)-\lambda\right)(-(\phi+z)-\lambda) - \varepsilon\frac{\rho(\alpha-\gamma\alpha)}{K(\psi+q)}\right] = 0$$

$$(-(\psi+q)-\lambda)\left[\left(\frac{(\sigma+\delta+\psi+u)(\psi+q)-\rho(\beta-\gamma\beta)}{\psi+q}\right)(\phi+z)+\lambda\left(\frac{(\sigma+\delta+\psi+u)(\psi+q)-\rho(\beta-\gamma\beta)}{\psi+q}\right)+\lambda(\phi+z)+\lambda^2-\varepsilon\frac{\rho(\alpha-\gamma\alpha)}{K(\psi+q)}\right]=0$$

that is

$$(-(\psi+q)-\lambda)\left[\lambda^2+\lambda\left(\frac{(\sigma+\delta+\psi+u)(\psi+q)-\rho(\beta-\gamma\beta)+(\phi+z)(\psi+q)}{\psi+q}\right)+\left(\frac{(\sigma+\delta+\psi+u)(\psi+q)-\rho(\beta-\gamma\beta)}{\psi+q}\right)(\phi+z)-\varepsilon\frac{\rho(\alpha-\gamma\alpha)}{K(\psi+q)}\right]=0 \quad (37)$$

Then

$$\lambda=-(\psi+q)$$

and

$$\left[\lambda^2+\lambda\left(\frac{(\sigma+\delta+\psi+u)(\psi+q)-\rho(\beta-\gamma\beta)+(\phi+z)(\psi+q)}{\psi+q}\right)+\left(\frac{(\sigma+\delta+\psi+u)(\psi+q)-\rho(\beta-\gamma\beta)}{\psi+q}\right)(\phi+z)-\varepsilon\frac{\rho(\alpha-\gamma\alpha)}{K(\psi+q)}\right]=0 \quad (38)$$

Obviously, one eigenvalue is negative. Now equation (38) is the characteristic equation of the sub matrix J_1, where

$$J_1=\begin{pmatrix}-\left(\frac{(\sigma+\delta+\psi+u)(\psi+q)-\rho(\beta-\gamma\beta)}{\psi+q}\right) & \frac{\rho(\alpha-\gamma\alpha)}{K(\psi+q)}\\ \varepsilon & -(\phi+z)\end{pmatrix} \quad (39)$$

If the trace of $J_1<0$ and the $\det(J_1)>0$ then the eigenvalues are negative

The trace of J_1 $=-\left(\frac{(\sigma+\delta+\psi+u)(\psi+q)-\rho(\beta-\gamma\beta)}{\psi+q}\right)-(\phi+z)$ (40)

$$=-(\sigma+\delta+\psi+u)(\psi+q)+\rho(\beta-\gamma\beta)-(\psi+q)(\phi+z)$$

$$=(\sigma+\delta+\psi+u)(\psi+q)\left[-1+\frac{\rho(\beta-\gamma\beta)}{(\sigma+\delta+\psi+u)(\psi+q)}\right]-(\psi+q)(\phi+z)$$

$$=(\sigma+\delta+\psi+u)(\psi+q)\left[-1+\left(R_0-\frac{\varepsilon\rho(\alpha-\gamma\alpha)}{K(\sigma+\delta+\psi+u)(\phi+z)(\psi+q)}\right)\right]-(\psi+q)(\phi+z) \quad (41)$$

<0, if $R_0<1$

and $det(J_1)=\frac{[(\sigma+\delta+\psi+u)(\psi+q)-\rho(\beta-\gamma\beta)](\phi+z)}{\psi+q}-\varepsilon\frac{\rho(\alpha-\gamma\alpha)}{K(\psi+q)}>0$ (42)

that is

$$\frac{(\sigma+\delta+\psi+u)(\psi+q)(\phi+z)}{\psi+q} - \frac{\rho(\beta-\gamma\beta)(\phi+z)}{\psi+q} - \frac{\varepsilon\rho(\alpha-\gamma\alpha)}{\mathrm{K}(\psi+q)} > 0$$

$$(\sigma+\delta+\psi+u)(\phi+z) - \left[\frac{\rho(\beta-\gamma\beta)(\phi+z)}{\psi+q} + \frac{\varepsilon\rho(\alpha-\gamma\alpha)}{\mathrm{K}(\psi+q)}\right] > 0$$

that is,

$$1 - \frac{\rho(\beta-\gamma\beta)}{(\psi+q)(\sigma+\delta+\psi+u)} + \frac{\varepsilon\rho(\alpha-\gamma\alpha)}{\mathrm{K}(\sigma+\delta+\psi+u)(\phi+z)(\psi+q)} > 0 \qquad (43)$$

$$1 - R_0 > 0$$

if

$$R_0 < 1$$

Thus, since all the eigenvalues of the characteristic equation (38) have negative real part, and the local asymptotically stability of $\mathbf{E_0}$ is proved.

Global Stability of Stability (GAS) of Disease Free Equilibrium (DFE) State

To ensure that the cholera infection eradication is independent of initial sizes of the population of the model, it is imperative to show that the DFE of the model (1) – (3), given by $\mathbf{E_0}$, is globally asymptotically stable.(GAS). To achieve this, we will use the following result introduced by (Castillo-Chevez et al, 2002).

Lemma 5. (Castillo-Chevez et al., 2002) Let system (27) – (28) be written in the form:

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

$$\frac{\mathrm{dZ}}{dt} = G(X,Z), \quad G(X,0) = 0 \qquad (44)$$

Where $X \in \mathbb{R}^m$ denotes (its components) the number of uninfected individuals and $Z \in \mathbb{R}^n$ denotes (its components) the number of infected individuals including latent, infectious, etc.; $\mathbf{E_0} = (X^*, 0)$, $X^* = \left(\frac{\rho}{\psi+q}\right)$, denotes the disease free equilibrium state of the system (27) – (29).

Also assume, the conditions (H_1) and (H_2) below

(H_1) For $\frac{\mathrm{dX}}{dt} = F(X,0)$, X^* is globally asymptotically stable (GAS).

(H_2) $G(X,Z) = AZ - \hat{G}(X,Z)$, $\hat{G}(X,Z) \geq 0$ for $(X,Z) \in \Omega$

where the jacobian $A = \frac{\partial G}{\partial Z}(X^*, 0)$ is an M-matrix (the off diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense.

Then the DFE state, $\mathbf{E_0} = (X^*, 0)$ is globally stable provided that $R_0 < 1$.

Theorem 6. The disease free equilibrium (DFE) state of the model (27) – (29) is globally asymptotic stable (GAS) if $R_0 < 1$.

Proof:

We only need to show that conditions (H_1) and (H_2) holds when $R_0 < 1$.

In our system (1) – (3), since $X = (S)$, $G = (I, B)$ and $X^* = \left(\frac{\rho}{\psi+q}\right)$, then

$$F(X,0) = [\rho - (\psi+q)S]$$

$$G(X,Z) = \begin{bmatrix} (\alpha-\gamma\alpha)\frac{\mathrm{B}}{\mathrm{K+B}}S + (\beta-\gamma\beta)SI - (\sigma+\delta+\psi+u)I \\ \varepsilon I - (\phi+z)\mathrm{B} \end{bmatrix}$$

We then obtain

$$A = \begin{pmatrix} \frac{\rho(\beta-\gamma\beta)}{\psi+q} - (\sigma+\delta+\psi+u) & \frac{\rho(\alpha-\gamma\alpha)}{K(\psi+q)} \\ \varepsilon & -(\phi+z) \end{pmatrix}$$

Which is clearly an M-matrix. Meanwhile

$$\hat{G}(X,Z) = \begin{pmatrix} (\alpha-\gamma\alpha)\frac{B^2}{K(K+B)}S \\ 0 \end{pmatrix}$$

Since $0 \leq S \leq \frac{\rho}{\psi+q}$, it is obvious that $\hat{G}(X,Z) \geq 0$.

The conditions (H_1) and (H_2) have been met and therefore E_0 is globally asymptotically stable.

Existence and Stability of endemic equilibria

Let $E_1 = (S^*, I^*, B^*)$ represent any arbitrary equilibrium of the system (27) – (29). The objective is to determine the number of possible endemic equilibria the system (27) – (29) can have when $R_0 > 1$.

Theorem 7. The system (27) – (29) has a unique endemic equilibrium whenever $R_0 > 1$, and no endemic equilibrium otherwise.

Proof:

Solving the model (27) – (29) at the steady-state gives

$$B^* = \frac{\varepsilon I^*}{(\phi+z)} \tag{45}$$

$$S^* = \frac{(\sigma+\delta+\psi+u)[K(\phi+z)+\varepsilon I^*]}{(\alpha-\gamma\alpha)\varepsilon+[K(\phi+z)+\varepsilon I^*](\beta-\gamma\beta)} \tag{46}$$

Substituting equations (45) and (46) into equation (27) gives

$$b_1 I^{*2} + b_2 I^* + b_3 = 0 \tag{47}$$

where

$$b_1 = -(\sigma+\delta+\psi+u)(\beta-\gamma\beta)\varepsilon$$
$$b_2 = \rho\varepsilon(\beta-\gamma\beta) - (\sigma+\delta+\psi+u)[(\psi+q)\varepsilon + (\alpha-\gamma\alpha)\varepsilon + (\beta-\gamma\beta)K(\phi+z)]$$
$$b_3 = \rho(\alpha-\gamma\alpha)\varepsilon + \rho K(\phi+z)(\beta-\gamma\beta) - (\sigma+\delta+\psi+u)(\psi+q)K(\phi+z)$$
$$= (\sigma+\delta+\psi+u)(\psi+q)K(\phi+z)[R_0-1]$$

The endemic equilibrium of the system (27) – (29) exists if the roots of equation (47) are real and positive. We use the Descartes rule of sign (Wang, 2004) to determine if positive roots exist. Since the sign of b_1 is negative and b_3 is positive for $R_0 > 1$, it follows that the model has a unique endemic equilibrium whenever $R_0 > 1$.

Sensitivity analysis of R_0 with respect to the control parameters

We carried out sensitivity analysis on the basis of the model parameter (Table 1) by the normalized forward sensitivity indices (Chitnis et al., 2006; Wu et al., 2013) using the following formula:

$$\Lambda_\nu^{R_0} = \left(\frac{\partial R_0}{\partial \nu}\right)\left(\frac{\nu}{R_0}\right)$$

where ν denotes the model parameter.

The sensitivity index of R_0, with respect to each parameter is given in Table 2.

Table 2. Sensitivity indices of R_0

Parameter	Description	Sensitivity indices
ρ	Recruitment rate	1.0000
α	Rate of injecting V. Cholerae from contaminated sources	1.0000
K	Concentration of Vibrio Cholerae in food and water that yield 50% chance of catching cholera disease.	-1.0000
β	human –to- human transmission rate	1.0000
γ	Public health education campaign rate	-0.0205
ψ	Human death rate	-0.9630
q	Vaccination rate	-0.6154
σ	Recovery rate of infected human	-1.5504
δ	Disease induced death rate	-0.1008
u	Treatment rate	-0.0775
ε	The rate of shedding of V.Cholerae by humans through untreated wastes	1.0000
Φ	Natural death rate of V.Cholerae	-0.9706
z	Water sanitation rate	-0.0294

It is shown from Table 2, that the threshold R_0, is sensitive proportionally to the changes in the parameter values of $\rho, \alpha, \beta,$ and ε. It implies that an increase (or decrease) in the value of each of the parameter in this case will lead to an increase (or decrease) in R_0 of the model (1) – (3). On the contrary, the threshold, R_0, is sensitive inversely proportional to the variation in the values of $K, \gamma, \psi, q, \sigma, \delta, u, \Phi,$ and z. In other words, an increase (or decrease) in the value of each of the parameter in this case leads to a corresponding decrease (or increase) in R_0.

Numerical Simulations

Numerical simulations for the model (1) - (4) are carried out, using the parameters in Table 2, unless otherwise stated, to illustrate some of the-analytical results established in this study.

The numerical simulations were conducted using the Runge-Kuta method (RK4) embedded in MATLAB.

Baseline Parameter Values

We show a baseline table for the parameters used in this model. The sources are also stated.

Table 3: Baseline Parameter values for equations (1) – (3)

Parameters	Baseline value	Reference
ρ	9.13×10^{-3}	(Hartley et al., 2006)
α	0.214	(Falaye et al., 2018)
K	10^6cell/day	(Codeco, 2001)
β	0.02	(Hartley et al., 2006)
γ	0.02	Assumed
ψ	0.025	(Falaye et al., 2018)
q	0.04	Assumed
σ	0.2	(Hartley et al., 2006)
δ	0.013	(Wang et al., 2011)

u	0.02	Assumed
ε	10 cell/day	(Wang et al., 2011)
ϕ	0.33	(Misra et al., (2011)
z	0.01	Assumed

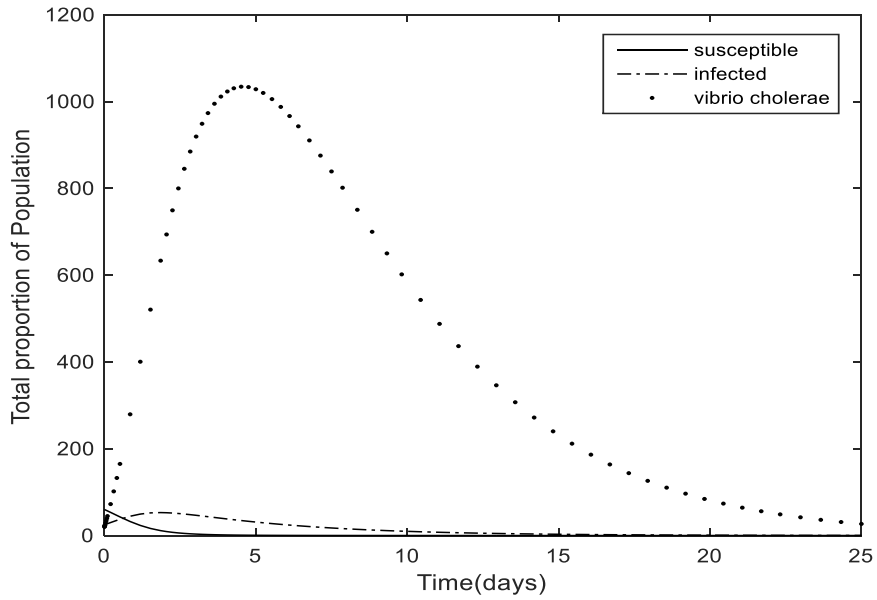

Figure 2: Graph of Susceptible and Infected individual in the population without control ($\gamma = 0, q = 0, u = 0, z = 0$) (presence of the bacteria *vibrio cholera*), $R_0 < 1$.

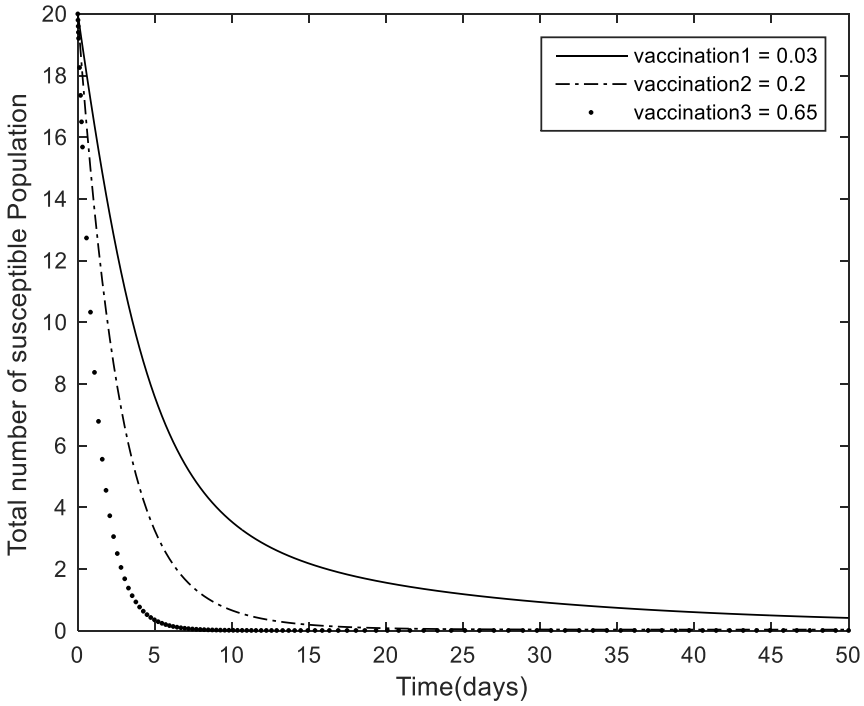

Figure 3: Effect of Vaccination ($q = 0.03; 0.2; 0.65$) of Susceptible individual without other control measures $(\gamma = 0, u = 0, z = 0)$. $R_0 < 1$.

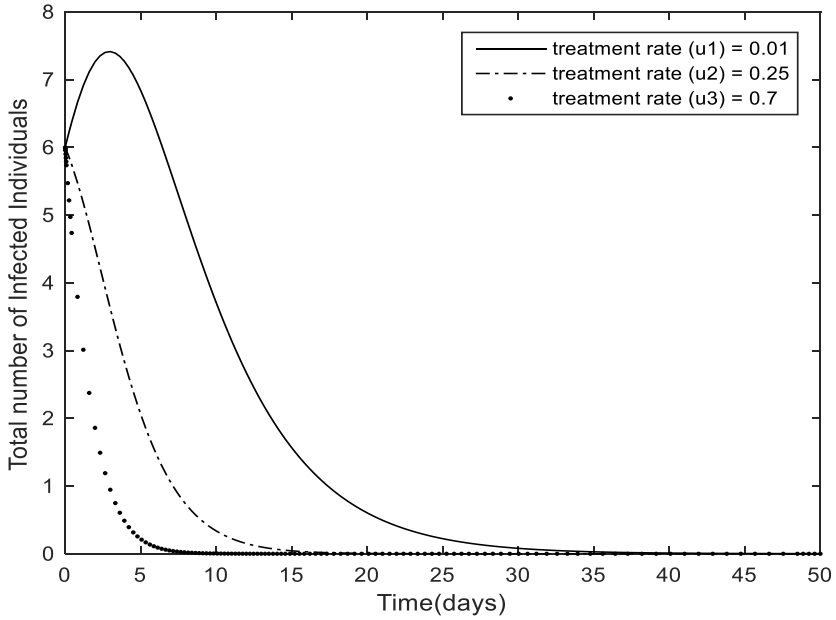

Figure 4: Effect of treatment $(u = 0.01, u = 0.25, u = 0.7)$ on infected individuals without other control measures $\gamma = 0, q = 0, z = 0)$, $R_0 < 1$.

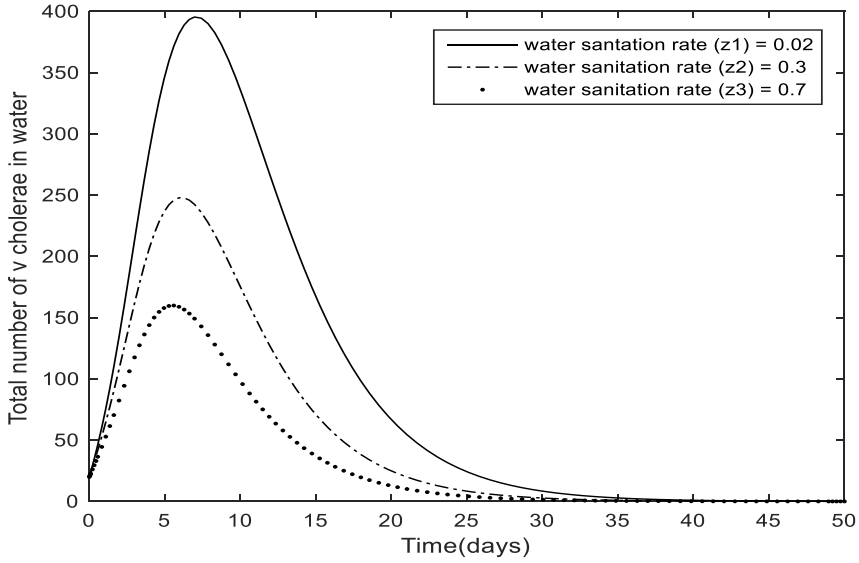

Figure 5: Effect of using different sanitation parameter values ($z = 0.02;\ 0.2;\ 0.7$) without other control measures ($\gamma = 0, q = 0, u = 0), R_0 < 1.$

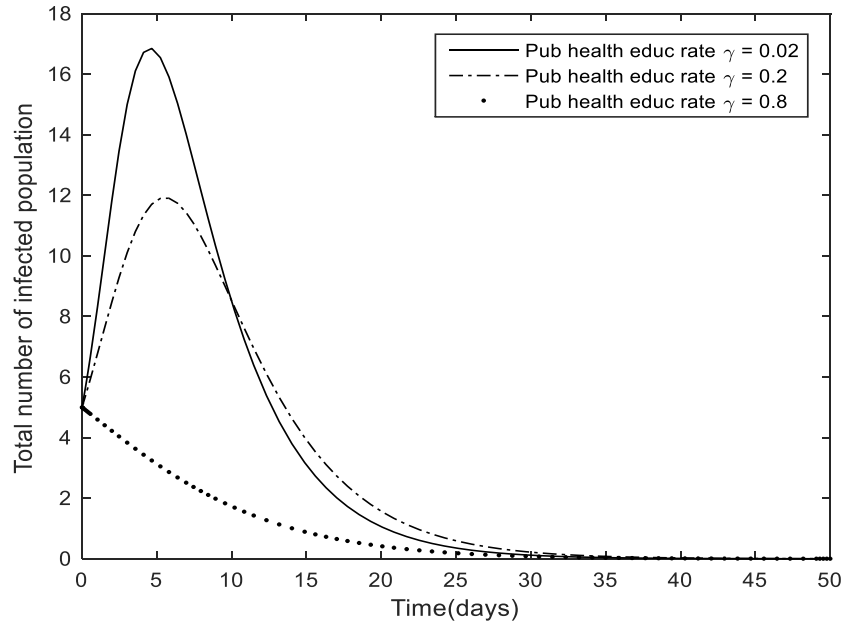

Figure 6: Effect of Public health education $(\gamma = 0.02; 0.2; 0.8)$, on infected individuals without other control measures $(z = 0, q = 0, u = 0)$ and $R_0 < 1.$

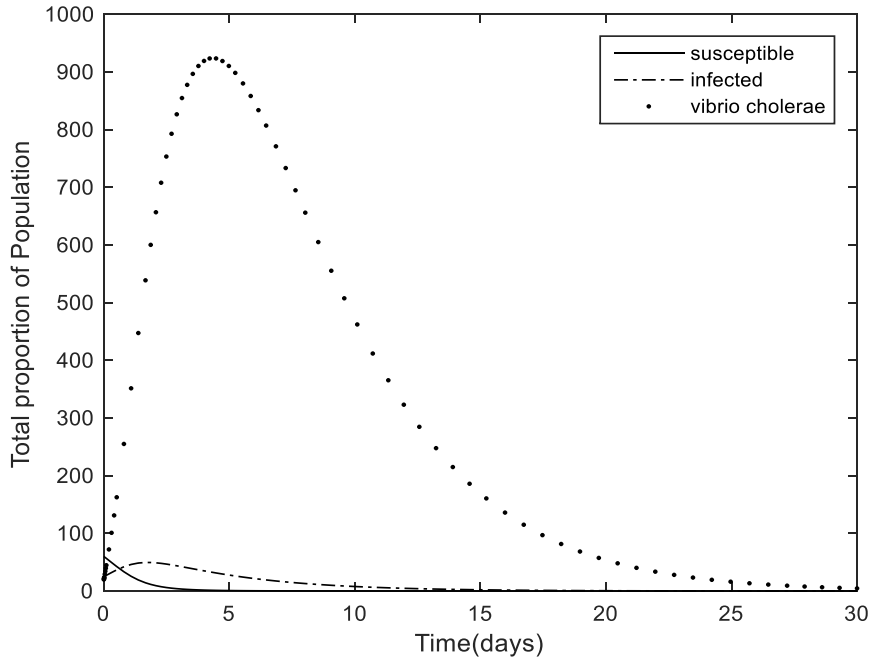

Figure 7: Graph of Susceptible and Infected individual in the population with weak controls (presence of the bacteria *vibrio cholera*) $\gamma = 0.02; q = 0.04; u = 0.02; z = 0.02, R_0 < 1$.

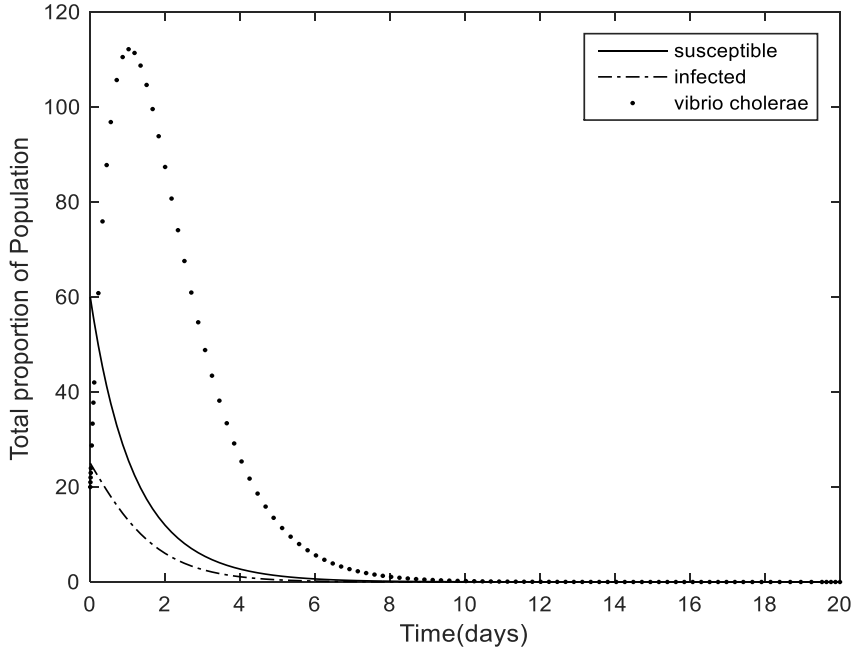

Figure 8: Graph of Susceptible and Infected individual in the population with strong controls (presence of the bacteria *vibrio cholera*), $\gamma = 0.7; q = 0.7; u = 0.65; z = 0.8, R_0 < 1$.

DISCUSSION OF RESULTS

The existence and uniqueness of the solution of the model was investigated using Theorem 1 and Theorem 2. Further qualitative analysis of the model shows that the solution of the model is bounded and positively invariant. The basic reproduction number of the model R_0, was computed using the next generation method given by

$R_0 = \frac{\rho(\beta-\gamma\beta)}{(\psi+q)(\sigma+\delta+\psi+u)} + \frac{\rho(\alpha-\gamma\alpha)\varepsilon}{K(\sigma+\delta+\psi+u)(\phi+z)(\psi+q)}$ as a threhold in the study of cholera infection both for predicting its outbreak and for evaluating its control strategies..

Stability analysis of the disease-free equilibrium state, DFEs, was explored using linearization method and taking R_0 as a threshold parameter. The results found in Theorem 4 and Lemma 5 shows that the disease-free equilibrium (DFE) state is locally as well as globally asympotically stable if the basic reproduction number is less than unity. The implication is that, cholera can be eliminated from the population if the initial sizes of the populations of the model are in the basin of attraction of the DFE, (E_0) (Theorem 4). The results from Lemma 5 shows the DFE, (E_0) is globally asympotically stable. This implies that elimination of cholera is independent of the initial sizes of the population.

Sensitivity analysis of R_0 with respect to the model parameters was carried out by the normalized forward sensitivity indices. The results of the sensitivity index of R_0, is given in Table 2. It is shown from Table 2, that the threshold R_0, is sensitive proportionally to the changes in the parameter values of ρ, α, β, and ε. It implies that an increase (or decrease) in the value of each of the parameter in this case will lead to an increase (or decrease) in R_0 of the model (1) – (3). On the contrary, the threshold, R_0, is sensitive inversely proportional to the variation in the values of $K, \gamma, \psi, q, \sigma, \delta, u, \phi,$ and z. In other words, an increase (or decrease) in the value of each of the parameter in this case leads to a corresponding decrease (or increase) in R_0. With reference to the four control parameters, vaccination rate with sensitivity index of (-0.6154) is the most sensitive control parameter for R_0, followed by treatment, sanitation and public health education campaign. These control parameters have an influence of minimizing cholera disease burden in the population as their values increases.

Various numerical simulations are carried out to assess the feasibility of eradication of cholera infection using the baseline parameter values in Table 3 and depicted in Figure 2 – Figure 8.

The simulation in Figure 6 shows prevalence of cholera infection in the human and pathogen population in the absence of any intervention $(q = 0,\ u = 0, z = 0, \gamma = 0)$. With the basic reproduction number $R_0 < 1$, in each case, shows convergence of the solution profile to the disease-free equilibrium (DFE). This is consistent with Theorem 4 and Lemma 5. Thus efforts geared at decreasing the infection transmission rate will play a significant role in eradicating cholera infection in the population.

The effect of single intervention strategy is displayed in Figure 3 – Figure 6. The burden of cholera infection in Figure 3 shows very significant decreasing cholera infection with increasing vaccination of susceptible individuals $(q = 0.03, 0.2, 0.7)$, while the infection transmission remain constant $(\alpha = 0.214, \beta = 0.02)$. Figure 4 display a substantive decline of cholera burden by increasing or improving treatment rate $(u = 0.01, 0.25, 0.7)$. Figure 5 also show a decreasing number of infected human by increasing the sanitation of contaminated water $(z = 0.02, 0.2, 0.7)$, while Figure 6 a decreasing cholera infection with increasing, expanded and consistent public health education campaigns.

Figure 7 and Figure 8 reveals the impact of combining the four intervention strategies with weak control and strong control measures. With a combination of weak controls $(q = 0.04, u = 0.02; z = 0.02, \gamma = 0.02)$, Figure 7 display a decreasing cholera burden in the population. With the basic reproduction number $R_0 < 1$, in each case, it also shows convergence of the solution profile to the disease-free equilibrium (DFE). This is consistent with Theorem 4 and Lemma 5.

With strong controls $(q = 0.7, u = 0.65; z = 0.8, \gamma = 0.7)$ Figure 8 further shows a decreasing cholera infection in the population. It further reveals, with the basic reproduction number $R_0 < 1$, in each case, it also shows a rapid convergence of the solution profile to the disease-free equilibrium (DFE) . Thus we can deduce from Figure 8 that with a combination of mass and consistent public health education campaigns, expanded vaccination coverage, prompt treatment of infected individuals, with water sanitation cholera infection can be eliminated from the population.

CONCLUSION

A deterministic epidemiological model of a cholera infection dynamics was presented. This study extended the model by Falaye et al, (2018) by incorporating four types of intervention strategies based on public health education campaigns, vaccination of susceptible human, treatment of infected humans and water sanitation.

The analysis of the model shows that there exist a unique solution that bounded and positively-invariant. The disease-free equilibrium (DFE) state of the model was determined and used to compute the basic reproduction number R_0, as a threhold in the study of cholera infection both for predicting its outbreak and for evaluating its control strategies. Stability analysis for the disease-free equilibrium state (DFEs) was carried out and the results shows that it is locally as well as globally asymptotically stable whenever the basic reproduction number $R_0 < 1$.

Sensitivity analysis of R_0 with respect to the model parameters was carried out. The results of the sensitivity index of R_0,shows that the threshold R_0, is sensitive proportionally to the changes in the parameter values of $\rho, \alpha, \beta,$ and ε. On the contrary, the threshold, R_0, is sensitive inversely proportional to the variation in the values of $K, \gamma, \psi, q, \sigma, \delta, u, \phi,$ and z. In other words, an increase (or decrease) in the value of each of the parameter in this case leads to a corresponding decrease (or increase) in R_0.

Numerical simulations of the model show that the infection transmission rate will play a significant role in eradicating cholera infection in the population. The effect of single intervention strategy also revealed that each of the control measures is vital in cholera eradication. It was further deduced that with a combination of mass and consistent public health education campaigns, expanded vaccination coverage, prompt treatment of infected individuals, with water sanitation cholera infection can be eliminated from the population in faster than single control strategy.

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