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MATHEMATICAL MODELLING OF CHOLERA TRANSMISSION DYNAMICS INCORPORATING VACCINATION

Abstract

A between-host and a within host cholera model incorporating vaccination by utilizing a system of differential equations to predict the spread of the disease and how it propagates in a human population is formulated. The formulated model is analyzed to determine the long-term solutions using classical mathematical analysis and numerical simulations using Mathematica and MATLAB softwares. Developing the appropriate mathematical model to be used in controlling cholera in a given population helps us to design precise and efficient strategy to control the infection when outbreaks occurs. The formulated model is analysed to determine the influence of its key parameters in the spread of the disease. We demonstrate that if the reproductive number, R_0, is less than one, the DFE is asymptotically stable and if $R_0 > 1$ the endemic equilibrium is asymptotically stable. Analysis of the model shows that R_0 is sensitive with respect to; recruitment to the population of the susceptible class, excretion of the vibrios to the environment, and transmission probability of unvaccinated individuals, while it is less sensitive to the rate of vaccination of the susceptible individuals, the death rate of vibrios, and rate of recovery from cholera infection.

Subject Classification: xxxxxx

Keywords: Sensitivity, Stability Analysis, Vaccination

1 Introduction

Cholera is an acute intestinal infection caused by the ingestion of food or water contaminated with the bacterium *Vibrio cholerae*. Once the bacteria

is ingested, it causes vomiting and watery diarrhoea leading to dehydration and eventually cause a drop in blood pressure and kidney failure. Watery loose bowels are the initial symptoms which appear in cholera patients. If not immediately treated, conceivable demise may happen within few days. The incubation period of cholera is between 24 hours and 5 days, see [1].

Cholera is transmitted through ingestion of food or water contaminated with the bacterium *Vibrio cholerae*. The infection is frequently asymptomatic. Not more than 25% of the infected persons become symptomatic; of these, 10–20% experience severe disease, see for instance [2]. The infection can spread rapidly in populations without safe drinking water, adequate sanitation and hygiene, and those with limited medical resources, see in [3]. Susceptible people traveling on a daily basis may contract the disease in destination sites and take the disease back to the possibly uninfected communities where they regularly live. At the same time, infected individuals not showing severe symptoms can carry the illness, thus releasing bacteria via their faeces, see for instance [4].

The World Health Organization (WHO) recommends the use of oral cholera vaccines, Dukoral and Shanchol for those at high risk, see [5]. Though these vaccines are considered to reduce the spread of cholera, they are documented not to be 100% effective and also wane with time in the human body, see in [3]. Thus, we develop a mathematical model to investigate the waning effect of the vaccine.

Mathematical models play a key role in cholera transmission by allowing researchers to simulate and predict the spread of the disease within a population. Epidemiologists and other researchers use mathematical modeling and numerical simulation for scientific understanding about the dynamics and preventive method of an infectious disease, for determining sensitivities, changes of parameter values, and to forecasting, see in [2]. Although models can be used to estimate the effectiveness of intervention strategies, many models tend to use one parameter to merge all the interventions. Though most models assume that vaccination has the same protective effect as natural immunity, in reality this is not true, since vaccinated individuals always go back for vaccination.

This paper is divided into sections. In section 1, we formulate the model and show that it is well-posed. In section 2.3 we analyse the long term solutions for DFE and EE respectively. Through local stability analysis, we show for each case how reproduction number R_0 is dependent on the parameters. We then proceed to show results for global behavior by use of appropriate Lyapunov functions.

2 Description and Formulation of the model

Let the total human population at time t be denoted by $N(t)$ and be divided into four compartmental sub-classes. Susceptible $S(t)$ denotes the size of the population at a time t that are not yet infected but maybe infected if exposed to Cholera; $V(t)$ are the number of individuals at a time t who are vaccinated; $I(t)$ the number of individuals at a time t who are infected with cholera, while $R(t)$ is the number of individuals who have recovered from cholera at a time t. Pathogen population is classified into two compartments, environmental pathogen denoted by $B(t)$, these are pathogens in the environment that can be contracted through ingestion of water or food that are contaminated with cholera causative agents (vibrio cholerae), while $Z(t)$ is the pathogen within the human body already fighting with human immunity. New recruitment (which is mainly by birth) is assumed to enter the population at a constant rate Λ, and ϕ is regarded as rate of vaccination. Assuming that the vaccine is imperfect, vaccinated individuals may become infected through contact with contaminated sources, thus, δ denotes the vaccine waning rate, in which $\delta \equiv 0$ means that the waning rate of the vaccine is high and individuals are at high risk of contracting the disease, while if $\delta \equiv 1$ implies that the waning rate of the vaccine is at low level and hence vaccine is completely effective in preventing infection.

Cholera transmission in this study is considered to be only through environment-to-human pathways, in particular, suscpetible individuals are infected by ingesting environmental vibrio-cholerae and the infection rates are $\beta_1 \frac{B}{K+B}$ and $\beta_2 \frac{B}{K+B}$ where β_1 is the probability of vaccinated individuals getting infected and β_2 is the transmission probability of unvaccinated individuals. The parameter K stands for carrying capacity of the pathogen while μ and d represents natural death rate and disease induced death rate respectively. The recovered group join the susceptible class at the rate denoted by η and infected cohort joins recovery class at the rate γ, α is the growth rate of human vibrios within the body, and ϵ is the rate at which vibrios is excreted to the environment. Finally, ψ is the intrinsic growth rate of human vibrios and ρ is the death rate of vibrios.

To develop the model, we make the following assumptions:-

(i) The recruitment into the population of study is mainly by birth, with all recruits assumed susceptible.

(ii) The transmission of cholera is assumed to be environment-to-person; that is, it is spread by consumption of food or drinking water that is contaminated by infected persons, see [6].

(iii) Since cholera vaccines are not 100% effective and wane with time, vaccinated individuals are considered to transit to become infective when in contact with the bacteria. Vaccination is meant to protect the susceptible from getting infected, however, when vaccinated and the efficacy of the vaccine wanes, then you contract the disease and become infected.

(iv) Recovered individuals become susceptible to the disease as there is no immunity benefit after recovery.

Taking into account the assumptions (i), (ii), (iii), and (iv) the schematic flow diagram in Figure 1 is plausible.

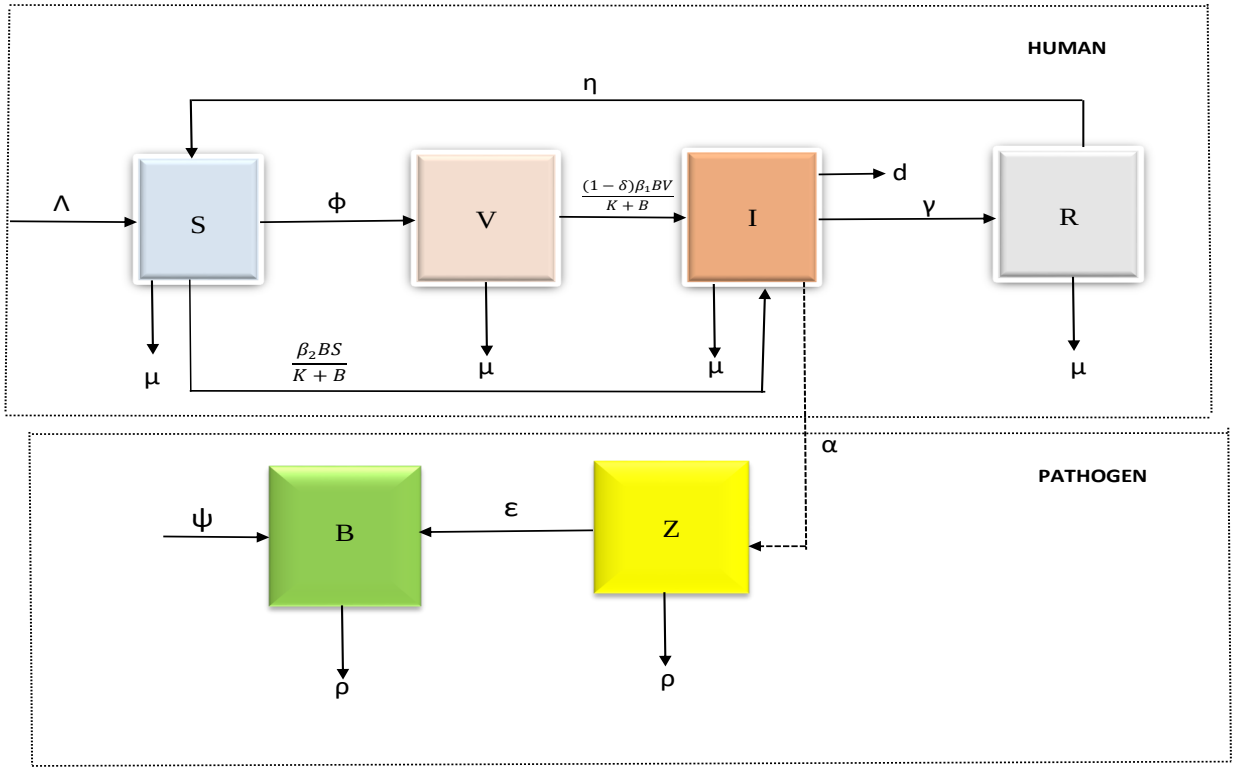

Figure 1: A Schematic Diagram of the Dynamics of cholera transmission

The arrows in Figure 1 indicate the transition from one state variable to another. Using the laws of mass action and assuming heterogeneous mixing the following system of equations is plausible:

$$\begin{aligned}
\dot{S} &= \Lambda - \phi S - \beta_2 \lambda(B) S - \mu S + \eta R, \\
\dot{V} &= \phi S - (1-\delta)\beta_1 \lambda(B) V - \mu V, \\
\dot{I} &= \beta_2 \lambda(B) S + (1-\delta)\beta_1 \lambda(B) V - (\mu + d + \gamma + \alpha) I, \\
\dot{R} &= \gamma I - (\mu + \eta) R,
\end{aligned}$$

$$\begin{aligned} \dot{Z} &= \alpha I - (\epsilon + \rho)Z, \\ \dot{B} &= \psi + \epsilon Z - \rho B, \end{aligned} \tag{1}$$

where: $\lambda(B) := \frac{B}{K+B}$ and $0 < \delta < 1$ is the waning rate of the vaccine. We observe from the second and third equations in Equation (1) that

$$\dot{V}|_{\delta=0} < \dot{V}|_{\delta=1}$$

and

$$\dot{I}|_{\delta=0} > \dot{I}|_{\delta=1}.$$

For the model to be biological feasible, we must show that it is well-posed and the solutions exists. Lets define a region Ω thus:

$$\Omega := \{(S, V, I, R, Z, B) \in \mathbb{R}^6_+ : (S, V, I, R) \leq \frac{\Lambda}{\mu},\ (Z, B) \leq \frac{\psi}{\rho})\}$$

Given initial data $(S(0), V(0), I(0), R(0), Z(0), B(0)) \in \mathbb{R}^6_+$, the solution of Equation (1) is bounded and remains positive for all $t \geq 0$ in the region Ω. We thus state and prove Lemma 1 for boundedness and apply Lemma 2 for positivity.

Lemma 1. *(Boundedness) The solution of Equation (1) with initial condition*

$$(S(0), V(0), I(0), R(0), Z(0), B(0)) \in \mathbb{R}^6_+$$

is bounded.

Proof. To show that the solution (S, V, I, R, Z, B) is bounded, the equation is split into two parts; namely, the total human population $S(t) + V(t) + I(t) + R(t) =: N(t)$, and the total pathogen population $Z(t) + B(t) =: N_B(t)$. Thus

$$\dot{N}(t) = \Lambda - \mu N(t) - (d + \alpha)I(t) \leq \Lambda - \mu N(t) \tag{2}$$

By the Variations-of-constants formula and comparison, we get:

$$\limsup_{t \longrightarrow \infty} N(t) \leq \frac{\Lambda}{\mu}. \tag{3}$$

Therefore $S(t), V(t), I(t)$ and $R(t)$ are ultimately bounded in $\mathbb{R}^4_+$. This implies that $(S(t), V(t), I(t), R(t))$, the human population under consideration is bounded. Adding the last two equations in Equation (1) and by the fact that $I < \frac{\Lambda}{\mu}$

$$\dot{N_B}(t) = \psi - \rho N_B(t) + \alpha I = (\psi + \frac{\alpha\Lambda}{\mu}) - \rho N_B(t). \tag{4}$$

By the Variations-of-constants formula and comparison, we have:

$$\limsup_{t\longrightarrow\infty} N_B(t) \leq (\psi - \frac{\alpha\Lambda}{\mu})/\rho \leq \frac{\psi}{\rho}.$$

Therefore $(Z(t), B(t))$ is ultimately bounded in $\mathbb{R}^2_+$. Hence the solution

$$(S(t), V(t), I(t), R(t), Z(t), B(t))$$

of Equation(1) is bounded. □

Lemma 2. *(Positivity) The solution of Equation (1), with initial conditions in the region Ω remains positive for all $t \geq 0$.*

Proof. We have
$\frac{dS(t)}{dt}|_{S=0} = \Lambda + \eta R > 0, \qquad \frac{dV(t)}{dt}|_{V=0} = \phi S > 0,$
$\frac{dI(t)}{dt}|_{I=0} = \beta_2 \frac{SB}{K+B} + (1-\delta)\beta_1 \frac{BV}{K+B} > 0, \qquad \frac{dR(t)}{dt}|_{R=0} = \gamma I > 0,$
$\frac{dZ(t)}{dt}|_{Z=0} = \alpha I > 0, \qquad \frac{dB(t)}{dt}|_{B=0} = \psi + \epsilon Z > 0.$
Hence all solutions of Equation (1) remain positive for all $t \geq 0$. □

Thus, by Lemma 1 and Lemma 2, the region Ω is positively invariant under the flow defined by Equation (1) and thus the model is mathematically and epidemiologically well-posed.

2.1 Equilibrium Points

The long-term solutions, are manifested in the two types of equilibrium points of interest, namely; Disease Free Equilibrium(DFE) point (in the absence of the disease) and Endemic Equilibrium(EE) point (in the presence of the disease).

At DFE, $S \neq 0, V \neq 0, I = 0, R = 0, Z = 0$ and $B = 0$. The model developed in Equation (1) has a DFE given by:

$$E_0 := \left(\frac{\Lambda}{\mu+\phi}, \frac{\phi\Lambda}{\mu(\phi+\mu)}, 0, 0, 0, 0\right). \tag{5}$$

To obtain the EE state, all the state variables are non zero, hence we have;

$$\begin{aligned} S^* &= \frac{\Lambda(\eta+\mu)\Big(\mu + (1-\delta)\beta_1\lambda(B^*)\Big)Y}{\Theta}, \quad V^* = \frac{\phi S^*}{\mu + (1-\delta)\beta_1\lambda(B^*)}, \\ I^* &= \frac{\Lambda(\eta+\mu)\Big((\mu + (1-\delta)\beta_1\lambda(B^*))\beta_2\lambda(B^*) + (1-\delta)\beta_1\lambda(B^*)\phi\Big)}{\Theta} \\ R^* &= \frac{\gamma I^*}{\eta+\mu}, \quad Z^* = \frac{\alpha I^*}{\epsilon+\rho}, \quad B^* = \frac{\psi}{\rho} + \frac{\epsilon Z^*}{\rho}, \end{aligned} \tag{6}$$

where, $Y := d + \alpha + \gamma + \mu$, and

$$\Theta := \gamma\eta(\delta-1)\phi\beta_1\lambda(B^*)+\Big(\mu+(1-\delta)\beta_1\lambda(B^*)\Big)\Big((\mu+\phi+\beta_2\lambda(B^*))(\eta+\mu)Y-\gamma\eta\lambda(B^*)\beta_2\Big).$$

2.2 Reproduction number

Using the next generation matrix method, as described in [7], we denote the rate of increase of secondary infection at the i^{th} disease compartment by F_i and V_i be the rate of disease progression in the i^{th} compartment. The i component represents the disease compartment and j represents the non-disease compartment. Taking the derivatives of Equation(1) with respect to the state variables at DFE(E_0), the matrices F and V are obtained and defined thus:

$$F := \left(\frac{\partial \mathcal{F}_i(E_0)}{\partial x_j}\right), \quad V := \left(\frac{\partial \mathcal{V}_i(E_0)}{\partial x_j}\right). \tag{7}$$

The $\mathcal{F}_i$ are the new infections (Transmission) while the $\mathcal{V}_i$ are the transfers of infection (Transition) from one compartment to another. Thus using Equation (1), Equation (7) gives,

$$\mathcal{F} := \begin{pmatrix} \beta_2 S\lambda(B) + (1-\delta)\beta_1 V\lambda(B) \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad \mathcal{V} := \begin{pmatrix} (\mu+d+\gamma+\alpha)I(t) \\ -\gamma I(t) + (\eta+\mu)R(t) \\ -\alpha I(t) + (\epsilon+\rho)Z(t) \\ -\epsilon Z(t) + \rho B(t) \end{pmatrix}. \tag{8}$$

Hence, the transmission matrix F and the Transition matrix V are:-

$$F := \begin{pmatrix} 0 & 0 & 0 & \beta_2 S\lambda'(B) - (1-\delta)\beta_1 V\lambda'(B) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad V := \begin{pmatrix} Y & 0 & 0 & 0 \\ -\gamma & (\mu+\eta) & 0 & 0 \\ -\alpha & 0 & (\epsilon+\rho) & 0 \\ 0 & 0 & -\epsilon & \rho \end{pmatrix}, \tag{9}$$

where $\lambda'(B) = \frac{K}{(K+B)^2}$, and the next generation matrix FV^{-1} is

$$FV^{-1} := \begin{pmatrix} \Big[\beta_2 S\lambda'(B) + (1-\delta)\beta_1 V\lambda'(B)\Big]\Big[\frac{\alpha\epsilon}{\rho(\epsilon+\rho)Y}\Big] & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}. \tag{10}$$

The reproduction number R_0 is thus given by $R_0 = \rho(FV^{-1})$ as described in [8], where $\rho(FV^{-1})$ is the spectral radius of the matrix (FV^{-1}) computed at E_0. Hence,

$$R_0 = \frac{\alpha\epsilon}{\rho(\epsilon+\rho)Y}\Big[\frac{\beta_2\Lambda}{K(\phi+\mu)} + (1-\delta)\frac{\beta_1\phi\Lambda}{K\mu(\mu+\phi)}\Big]. \tag{11}$$

3 Stability Analysis

Stability analysis is the process of determining the behavior of a system over time. In this section, local and global stability analysis of the Disease Free Equilibrium and Endemic Equilibrium is done.

3.1 Local Stability Analysis of the Disease Free Equilibrium

In this section, local stability of the Disease Free Equilibrium (DFE) E_0 for Equation(1) is obtained. DFE is an equilibrium point at which the population remains in absence of the cholera disease and is characterized by the nonexistence of infected nodes. To investigate the local stability of the DFE, we make the following Proposition (1).

Proposition 1. *If* $R_0 < 1$, *then* $E_0 = \left(\frac{\Lambda}{\mu+\phi}, \frac{\phi\Lambda}{\mu(\phi+\mu)}, 0, 0, 0, 0\right) \in \Omega$ *is an equilibrium state that is locally asymptotically stable.*

Proof. The Jacobi matrix of Equation (1) at E_0 is:

$$J(E_0) = \begin{pmatrix} -\phi-\mu & 0 & 0 & \eta & 0 & -\frac{\beta_2\Lambda}{K(\phi+\mu)} \\ \phi & -\mu & 0 & 0 & 0 & -(1-\delta)\frac{\beta_1\phi\Lambda}{K\mu(\phi+\mu)} \\ 0 & 0 & -Y & 0 & 0 & \frac{\beta_2\Lambda}{K(\phi+\mu)} + (1-\delta)\frac{\beta_1\phi\Lambda}{K\mu(\phi+\mu)} \\ 0 & 0 & \gamma & -(\mu+\eta) & 0 & 0 \\ 0 & 0 & \alpha & 0 & -(\epsilon+\rho) & 0 \\ 0 & 0 & 0 & 0 & \epsilon & -\rho \end{pmatrix}. \tag{12}$$

where $Y = \mu + d + \gamma + \alpha$.

Three of its eigenvalues are $-(\phi+\mu), -\mu, -(\mu+\eta)$, and the other three eigenvalues are obtained from the following reduced matrix

$$J_1(E_0) := \begin{pmatrix} -Y & 0 & \frac{\beta_2\Lambda}{K(\phi+\mu)} + (1-\delta)\frac{\beta_1\phi\Lambda}{K\mu(\phi+\mu)} \\ \alpha & -(\epsilon+\rho) & 0 \\ 0 & \epsilon & -\rho \end{pmatrix}. \tag{13}$$

Applying Hurwitz Criterion, see for instance [**?**], the trace of $J_1(E_0)$ is

$$-\rho - Y - (\epsilon+\rho) \tag{14}$$

and is negative while its determinant is positive if

$$\frac{-\beta_2\epsilon\alpha\Lambda}{K\rho(\phi+\mu)} - \epsilon\alpha(1-\delta)\frac{\beta_1\phi\Lambda}{k\mu\rho(\phi+\mu)} + Y(\epsilon+\rho) > 0. \tag{15}$$

Using the expression of R_0, as described in Equation (11), Equation (15) reduces to

$$Y(\epsilon+\rho)(1-R_0) > 0 \tag{16}$$

hence guarantees local asymptotic stability if $1 - R_0 > 0$. □

3.2 Global Stability Analysis of the Disease Free Equilibrium

The global asymptotic stability of the disease free equilibrium is analyzed using a theorem by Castillo Chavez *et. al* [9].

Equation (1) is rewritten in the form

$$\frac{dX(t)}{dt} = F(X(t), W(t)), \quad \frac{dW(t)}{dt} = G(X(t), W(t)), \quad G(X(t), 0) = 0 \tag{17}$$

where $X(t) := (S(t), V(t))$ and $W(t) := (I(t), R(t), Z(t), B(t))$, with $X(t) \in \mathbb{R}^2_+$ denoting the total numbers in the uninfected compartments and $W(t) \in \mathbb{R}^4_+$ denoting the number in the infected compartments. The disease free equilibrium is now denoted by

$$U_0 := (X_0, O) \quad \text{with} \quad X_0 := (\frac{\Lambda}{\phi + \mu}, \frac{\Lambda\phi}{\mu(\phi + \mu)}), \; O = (0, 0, 0, 0)$$

Consider the conditions $\mathbf{H_1}$ and $\mathbf{H_2}$

$\mathbf{H_1}$: For $\frac{dX(t)}{dt} = F(X(t), 0)$, X_0 is Globally Asymptotically Stable,

$\mathbf{H_2}$: For $G(X(t), W(t)) = AW(t) - \hat{G}(X(t), W(t))$, $\hat{G}(X(t), W(t)) \geq 0$, for $((X(t), W(t)) \in \Omega$ where $A = D_W G(U_0, 0)$ is a metzler matrix; that is, the off diagonal elements of A are non-negative.

Theorem 1. *Assume* $\mathbf{H_1}$ *and* $\mathbf{H_2}$ *are satisfied, the fixed point* $U_0 = (X_0, 0)$ *is a Globally Asymptotically Stable equilibrium of Equation (1) provided* $R_0 < 1$. *Furthermore,* R_0 *is asymptotically decreasing with respect to* δ

Proof. We have

$$\frac{dX(t)}{dt} := F(X(t), W(t)) = \begin{pmatrix} \Lambda - \phi S - \beta_2 S\lambda(B) - \mu S + \eta R \\ \phi S - (1-\delta)\beta_1 B\lambda(B)V - \mu V \end{pmatrix} \tag{18}$$

$$F(X(t), 0) = (\Lambda - \mu S(t) - \phi S, \phi S - \mu V, 0) \tag{19}$$

$$\frac{dW(t)}{dt} = G(X(t), W(t)) := \begin{pmatrix} (1-\delta)\beta_1 V\lambda(B) - YI \\ \gamma I - (\mu + \eta)R \\ \alpha I - (\epsilon + \rho)Z \\ \psi + \epsilon Z - \rho B \end{pmatrix} \tag{20}$$

and $G(X(t), 0) = 0$.

Therefore,

$$\frac{dX(t)}{dt} = F(X(t), 0) = \begin{pmatrix} \Lambda - \phi S - \mu S \\ \phi S - \mu V \end{pmatrix} \tag{21}$$

$$A = D_W G(X_0, 0) = \begin{pmatrix} -Y & 0 & 0 & \frac{\beta_2 \Lambda}{K(\phi+\mu)} + (1-\delta)\frac{\beta_1 \phi \Lambda}{k\mu(\phi+\mu)} \\ \gamma & -(\mu+\eta) & 0 & 0 \\ \alpha & 0 & -(\epsilon+\rho) & 0 \\ 0 & 0 & \epsilon & -\rho \end{pmatrix}, \tag{22}$$

$$\text{and } \hat{G}(X(t), W(t)) = \begin{pmatrix} \hat{G}_1(X(t), W(t)) \\ \hat{G}_2(X(t), W(t)) \\ \hat{G}_3(X(t), W(t)) \\ \hat{G}_4(X(t), W(t)) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{23}$$

It follows that $\hat{G}_1(X(t), W(t)) \geq 0$, $\hat{G}_2(X(t), W(t)) = \hat{G}_3(X(t), W(t)) = \hat{G}_4(X(t), W(t)) = 0$ thus $\hat{G}(X(t), W(t)) \geq 0$. Conditions $\mathbf{H_1}$ and $\mathbf{H_2}$ are thus satisfied and hence U_0 is Globally Asymptotically Stable for $R_0 < 1$.

□

Global asymptotic stability shows that regardless of any initial solution by the introduction of any given number of infectives in the population, the solutions of the model will always converge to DFE whenever $R_0 < 1$.

3.3 Stability Analysis of the Endemic Equilibrium

The Endemic Equilibrium (EE)state is the state where the disease cannot be totally eradicated but remains in the population at manageable levels. Cholera is endemic or persistent in the population if

$$E^* := (S^*(t), V^*(t), I^*(t), R^*(t), Z^*(t), B^*(t)) \in \Omega$$

for all $t > 0$. E^* is the endemic state of Equation (1). To investigate the local stability of the EE, Proposition 2 is made.

Proposition 2. *If $R_0 > 1$, then E^* is an equilibrium state in Ω and is locally asymptotically stable.*

Proof. To investigate the stability of E^* of Equation (1), we determine the eigenvalues of the coefficient matrix $J(E^*)$ of the vector field in Equation (1) linearized at E^*,

$$-\Big(\phi+\beta_2\lambda(B^*)+\mu\Big),\ -\Big((1-\delta)\beta_1\lambda(B^*)+\mu\Big),\ -Y,\ -(\mu+\eta),\ -(\epsilon+\rho), \text{and} -\rho. \tag{24}$$

where B^* is given as,

$$B^* = \frac{\psi}{\rho} + \frac{\alpha\epsilon\Lambda(\eta+\mu)}{\rho\eta\gamma(\epsilon+\rho)}\Big[-1 - \frac{(\eta+\mu)Y(\mu-(1-\delta)\lambda(B^*)\beta_2)(\mu+\phi+\lambda(B^*)\beta_1)}{\Theta}\Big], \tag{25}$$

For asymptotic stability, all the eigenvalues should be negative. The first two eigenvalues will remain negative whenever $R_0 > 1$.

□

Epidemiologically, if $R_0 > 1$, then each infected individual in the entire period of infectivity will produce more than one infected individual on average, which shows the disease will persist in the population.

3.4 Global Stability Analysis of the Endemic Equilibrium

In this section, Lyapunov function is used to analyse the global stability of the endemic equilibrium E^* under the condition $R_0 > 1$.

Theorem 2. *The endemic equilibrium E^* of the model in Equation (1) is globally asymptotically stable in Ω whenever $R_0 > 1$.*

Proof. Consider the following Lyapunov function;

$$C := S - S^* \ln(S) + V - V^* \ln(V) + I - I^* \ln(I) + R - R^* \ln(R) + Z - Z^* \ln(Z + B - B^* \ln(B) \quad (26$$

Differentiating C with respect to t gives:-

$$\dot{C} = \left(1 - \frac{S^*}{S}\right)\dot{S} + \left(1 - \frac{V^*}{V}\right)\dot{V} + \left(1 - \frac{I^*}{I}\right)\dot{I} + \left(1 - \frac{R^*}{R}\right)\dot{R} + \left(1 - \frac{Z^*}{Z}\right)\dot{Z} + \left(1 - \frac{B^*}{B}\right)\dot{B} \quad (27)$$

Using Equation (1) in Equation (27)and noting that at the boundary $S \leq \frac{\Lambda}{\mu+\phi}$, $V \leq \frac{\phi\Lambda}{\mu(\phi+\mu)}$, $S = S^*, V = V^*, I = I^*, R = R^*, Z = Z^*$, and $B = B^*$. The inequality $\dot{C} \leq 0$ holds iff (S, V, I, R, Z, B) takes the equilibrium values $(S^*, V^*, I^*, R^*, Z^*, B^*)$. Clearly at the boundary, Equation (27) becomes;

$$\dot{C} = 0 \quad (28)$$

Therefore, by Lassalles's invariance principle, see for instance [10], the endemic equilibrium E^* is Globally Asymptotically stable. □

This is significant to epidemiologists, as the conditions required for stability of the model ($R_0 < 1$) will provide a basis for the necessary indicators to be controlled in the reduction of the transmission of Cholera.

4 Sensitivity Analysis

Normalized forward sensitivity index also known as elasticity, as described in [11], is used to analyse the sensitivity of R_0. The normalized forward sensitivity

index of the reproduction number R_0 with respect to a parameter value P is given by;

$$\Gamma_P^{R_0} = \frac{\partial R_0}{\partial P} \times \frac{P}{R_0}. \tag{29}$$

For $R_0 = \frac{\alpha\epsilon}{\rho(\epsilon+\rho)(\mu+d+\gamma+\alpha)}\left[\frac{\beta_2\Lambda}{K(\phi+\mu)} + (1-\delta)\frac{\beta_1\phi\Lambda}{K\mu(\mu+\phi)}\right]$, we have

$$\begin{aligned}
\Gamma_{\beta_1}^{R_0} &= \frac{\beta_1(1-\delta)\phi}{\beta_2\mu + (1-\delta)\beta_1\phi}, \quad \Gamma_{\beta_2}^{R_0} = \frac{\beta_2\mu}{\beta_2\mu + (1-\delta)\beta_1\phi}, \quad \Gamma_{\delta}^{R_0} = -\frac{\beta_1\phi\delta}{\beta_2\mu + (1-\delta)\beta_1\phi}, \\
\Gamma_{\phi}^{R_0} &= \frac{-\beta_2\mu + (1-\delta)(\phi+\mu)\left[\beta_1\mu\right]}{\beta_2\mu + (1-\delta)\beta_1\phi}, \quad \Gamma_{\Lambda}^{R_0} = 1, \quad \Gamma_{K}^{R_0} = -1, \quad \Gamma_{\alpha}^{R_0} = 1 - \frac{\alpha}{\mu+d+\gamma+\phi}, \\
\Gamma_{\epsilon}^{R_0} &= 1 - \frac{\epsilon}{\epsilon+\rho}, \quad \Gamma_{\Gamma}^{R_0} = \frac{-\gamma}{\mu+d+\gamma+\alpha}, \quad \Gamma_{d}^{R_0} = \frac{-d}{\mu+d+\gamma+\alpha}, \quad \Gamma_{\rho}^{R_0} = -1 - \frac{\rho}{\epsilon+\rho} \\
\Gamma_{\mu}^{R_0} &= \frac{\beta_2\mu}{\beta_2\mu + (1-\delta)\beta_1\phi} - \frac{2\mu+\phi}{\mu+\phi} - \frac{1}{\mu+d+\gamma+\alpha}.
\end{aligned} \tag{30}$$

Using initial parameter values from literature, sensitivity indices are evaluated and summarized in Table 1.

Table 1: **Sensitivity indices of the reproduction number for model parameters**

Parameter	Value (Reference)	Sensitivity
Λ		1
ϵ	1.1 - 4.1 phage of particles per ml of watery stools ([13])	0.982
β_2	0.553 per year ([12])	0.6207
δ	after 3 years ([14])	0.5893
β_1	0.447 per year ([12])	0.3717
μ	0.015 per year ([15])	.0572
α	6-8 hours ([5])	-0.6100
d	0.017 per year ([5])	-0.3039
K		-1
γ	0 - 7 days within infected surfaces ([12])	-1.082
ρ	1.5 - 4 hours ([16])	-1.198
ϕ	1.7% uptake per year ([15])	-3.550

The results showed that the recruitment rate, excretion of vibrios to the environment, and transmission probability of unvaccinated individuals are the most sensitive parameters, significantly contributing to the increase in R_0.

The less sensitive parameters to R_0 were the rate of vaccination of the susceptible individuals, the death rate of vibrous, and rate of recovery from cholera infection. Additionally, differentiating R_0 with respect to δ, we obtain

$$\frac{\partial R_0}{\partial \delta} = -\frac{\alpha\epsilon\beta_1\Lambda\phi}{K\rho\mu(\epsilon+\rho)(\mu+d+\gamma+\alpha)(\mu+\phi)}$$

Since all the parameters are positive, then $\frac{\partial R_0}{\partial \delta} < 0$ implies that R_0 is a decreasing function with respect to δ. In addition, if $\frac{\partial R_0}{\partial \delta} < 0$, it means R_0 decreases with increase in the efficacy of the vaccine, and hence the spread of the disease is reduced.

5 Numerical Simulation of the Model

In this section, we use Matlab software to illustrate the numerical simulations describing the theoretical results for Equation (1). The following numerical values are used in the simulation of the model.

Table 2: **Parameter Estimates for the Model**

Description	**Parameters**	**Values**	**Source**
Recruitment rate	Λ	10,000 per year	Estimate
Probability of vaccinated individuals getting infected	β_1	[0.011-0.95] per year	[12],[4]
Transmission probability of un-vaccinated individuals	β_2	0.553 per year	[12]
Rate of vaccination of the Susceptibles	ϕ	1.7% per year	[15]
Mortality rate	μ	0.01562 per year	[4]
Waning rate of the vaccine	δ	after 3 years	[14]
Death rate due to the disease	d	6-8 hours	[5]
Rate of recovery from infection	γ	0 - 7 days within infected surfaces	[4]
Disease induced death rate	d	0.0013 per year	[4]
Rate of conversion of recovered individuals to susceptible	η	0.00042 per year	[5]
Intrinsic growth rate of human vibrios	ψ	0.45758	[4]
Death rate of vibrios	ρ	1.5- 4 hours	[16]
Growth rate of human vibrios within the body of infected individual	α	6 - 8 hours	[4]
Excretion of vibrios to the environment	ϵ	1.1-4.1 phage of particles per ml of watery stools	[20]

From Figure 2, even though there is vaccination, the number of cholera cases will always persists in the population.

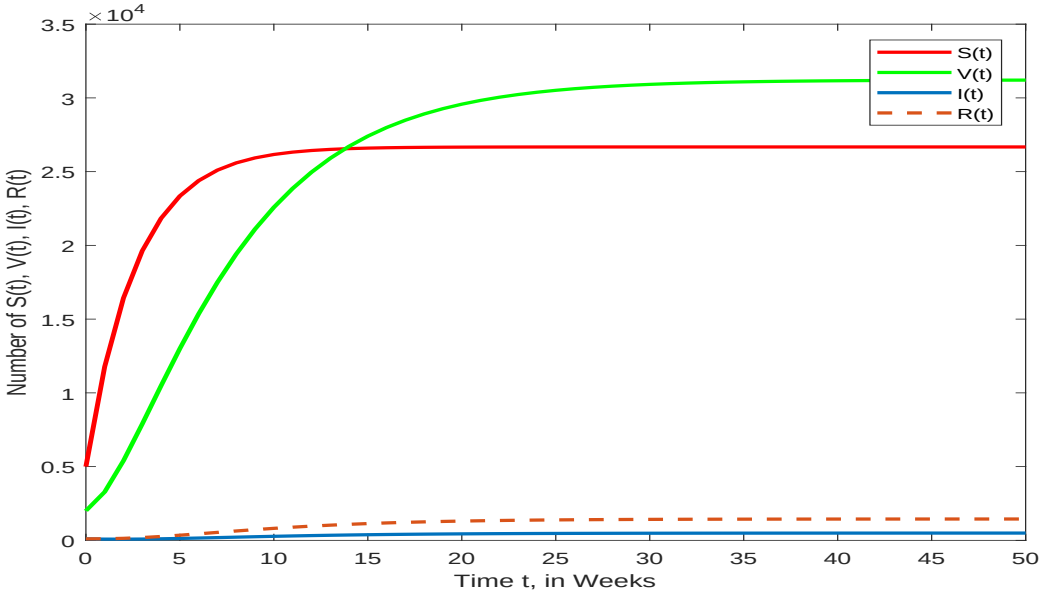

Figure 2: Simulation of the EE model

Although vaccination can improve the reduction of cholera cases, interventions such as hygiene enhancement, and sensitization of proper sanitation practices maybe necessary for the control and eradication of cholera disease.

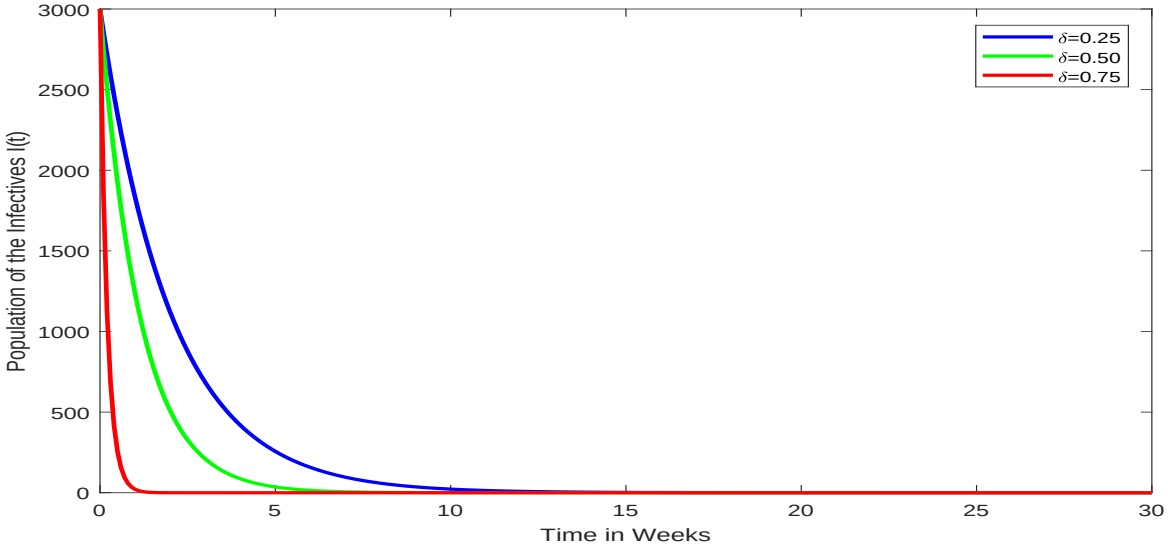

Figure 3: Simulation of infectives and waning effect of the vaccine.

Figure 3 shows that when δ is high (0.75) waning rate is low and hence the number of cholera infectives cases reduces in the population, while when δ is low(0.25) cholera cases will initially be high. This indicates that when the waning effect of the vaccine is high (the vaccine is ineffective)the number of cholera infectives in a given population is high, while if the waning effect is low (the vaccine is effective)the number of cholera infectives in the population decreases at a faster rate.

6 Conclusion

From the results, if the reproduction number R_0 is less than unity then the DFE is locally and globally asymptotically stable. Additionally, if $R_0 > 1$, the endemic equilibrium is asymptotically stable. The most sensitive parameters were; recruitment rate(Λ), rate of excretion of cholera vibrio to the environment (ϵ), and transmission probability of unvaccinated individuals (β_2), hence the advocacy of uptake of vaccination towards cholera will lead to reduction of cholera cases in a given population. The less sensitive parameters to R_0 were the rate of vaccination of the susceptible individuals (ϕ), the death rate of vibrous (ρ), and rate of recovery from cholera infection (γ). This shows that increasing these parameters will significantly lead to the reduction of R_0. The government should sensitize people living in risk prone areas to take up vaccination in order to boost their immune system to avoid more infections in the population in cases of an outbreak.

References

[1] Owade., Okaka A., Tireito F., (2023). Mathematical model on dynamics of in-host infection cholera disease with vaccination, *Discrete Dynamics in Nature and Society,* **(7)**, https://doi:10.1155/2023/1465228.

[2] Cui J., Xueyong Z., (2014). Mathematical analysis of a cholera model with vaccination *Journal of Applied Mathematics*, Wiley online library.

[3] Elimian, K. O., et al (2020). Identifying and quantifying the factors associated with cholera-related death during the 2018 outbreak in Nigeria, *Pan African Medical Journal,* **37(368)**, 1–13. https://doi.org/10.11604/PAMJ.2020.37.368.20981.

[4] Wang X. and Wang J., (2017). Disease dynamics in a coupled cholera model linking within host and between-host interactions, *J. Biol. Dyn.,*, **11**, 238-262.

[5] WHO (2017). World Health Organization (2017), Cholera vaccines, *WHO position paper,* **92(34)**, 477-500.

[6] Sinclair D, Abba K, Zaman K, Qadri F, Graves PM (2011). Oral vaccines for preventing cholera, *Cochrane Database Syst Rev.* (3).

[7] Van-den Driessche J., & Watmough J., (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission *Journal Math Biosci.* **180**, 29-48.

[8] Dieckmann U., Metz J., Sabelis M., & Sigmund K., (2002). *Adaptive dynamics of infectious diseases: In pursuit of virulence management.* New York, Cambridge University Press.

[9] Castillo-Chavez C., Zhilan F., and Wenzhan H., (2002). On the computation of reproduction number and its role in global stability, Mathematical approaches for emerging and re-emerging infectious diseases*Institute for Mathematics and Its applications,* **67**, 229-250.

[10] Lasalle, J., (1976). The stability of dynamical systems, *Regional Conference series in Applied Mathematics*, SIAM USA.

[11] Codeco C. (2001). Endemic and epidemic dynamics of cholera: the role of the aquatic reservoir, *BMC Infectious diseases*, **1**, 117-119.

[12] Amit S., Clement D., & Saha A.,(2024). Socio-economic drivers of vaccine uptake in Sub-Saharan Africa *National Center for Biotechnology Information.* **36(31)**, 4742-4749.

[13] Ahmed, I., Akgül, A., Jarad, F., Kumam, P. & Nonlaopon, K. (2023). A Caputo-Fabrizio fractional-order cholera model and its sensitivity analysis. *Mathematical Modelling and Numerical Simulation with Applications,* **3(2)**, 170-187.https://doi.org/10.53391/mmnsa.1293162.

[14] Cai L., Tuncer N., Martcheva M. (2017). How does within-host dynamics affect populationlevel dynamics? Insights from an immuno-epidemiological model of malaria, Math. *Methods Appl. Sci.*, **20**: 6424-6450.

[15] KDHS (2022). Kenya Demographic and Health Survey, *Key Indicators Report.* A summary Report.

[16] Nelson E, Harris J, Morris J, Calderwood S and Camilli A.(2009). Cholera transmission, the host, pathogen and bacteriophage dynamics, *Nature Rev. Microbiology*, **7**, 693-702.