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A Mathematical Model for Cholera Transmission Dynamics considering Primary and Booster Vaccinations as Controls

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ABSTRACT

Cholera is an acute diarrheal illness caused by infection with the bacteria vibrio cholerae. In this paper, a mathematical model for cholera transmission dynamics with an arbitrary contact rate function, considering primary and booster vaccinations as controls is formulated and analyzed. First, a constant contact rate function was assumed and the equilibrium analysis and numerical simulation were carried out. Secondly, a seasonally forced contact rate function was assumed and the numerical simulation was performed. In the first case, the analytical results showed that the disease-free (respectively endemic) equilibrium state is locally and asymptotically stable for $R_0 < 1$ (respectively$R_0 > 1$). These analytical results were also buttressed by the results of the numerical simulation. In the second case, the numerical results showed the seasonal variations in the number of infected people when there is no control. However, with effective primary and booster vaccinations, the spread of cholera can be controlled. The findings in this study suggest that effective primary and booster vaccination programs are crucial for the control of cholera.

Keywords: mathematical model, booster vaccination, disease-free equilibrium, endemic equilibrium

INTRODUCTION

Cholera is an acute diarrheal illness caused by infection of the intestine with the bacteria Vibrio cholerae. A person may get cholera by drinking or eating food that is contaminated with the cholera bacterium. The source of the contamination is usually faeces of an infected person or water contaminated with sewage. V. cholerae can also be found in

brackish rivers and coastal water. The V. cholerae bacterium thrives in an environment with poor sanitary conditions. In an infected person the V. cholerae bacterium accumulates in the person's stomach and produces toxins, which affect the cells of the gastrointestinal tract [WHO (2000), SDWF (2008), WHO (2011].

Common symptoms of cholera infection include profuse watery diarrhea, stomach aches, leg cramps, mild fever and vomiting which can result in severe dehydration or fluid loss (about one litre per hour). Death can occur within several hours because of rapid dehydration. The incubation period lies within several hours and five days [WHO (2000), HP (2011), SDWF (2008)].

Since the first emergence of cholera from the Ganges Delta of the Indian subcontinent in 1817, humanity has experienced seven pandemics. In recent times, cholera has been a threat to the developing countries in the tropical and sub-tropical regions of Asia, Africa and South and Central America where safe water and sanitation infrastructure are a challenge. For instance, 45 countries reported 190,130 cases (5143 deaths) and 221,226 cases (4,946 deaths) to WHO in 2008 and 2009 respectively [WHO (2011), HP (2011)]. As reported in HP (2011), Africa alone had 98% of the cholera cases (217,333 cases) and 99% of the deaths worldwide (4883 cases), while 1902 (0.86%) cases were reported from Asia. Of the 55 outbreaks of acute diarrhoea disease verified by WHO, 47 were confirmed as cholera outbreaks in 29 countries, of which 38 (80.8%) occurred in Africa and 9 (19.1%) in Asia. In recent years, massive and prolonged outbreaks have occurred in countries that have been free of cholera for decades. One of the large outbreaks took place in Zimbabwe resulting in 98,592 cases including 4288 deaths between August 2008 and July 2009. More recently, an outbreak of cholera broke out in Haiti following an earthquake that struck in early January 2010. As of June 4, 2011, the outbreak had resulted in over 331,454 cumulative cholera cases and 5386 deaths [HP (2011)].

Treatment, vaccine, water, sanitation and hygiene interventions are available. The primary treatment for the cholera patient is oral rehydration treatment (ORT). Oral cholera vaccines such as Dukarol or Shanchol are also available. Provision of safe water, sanitation and personal hygiene are all important measures that can stop cholera transmission. For details, see Fung (2014). The plan of this paper is as follows. Section 2 is devoted to model formulation and analysis. Numerical simulations are performed in section 3. Discussion and conclusive remarks are passed in sections 4 and 5 respectively.

MODEL FORMULATION AND ANALYSIS

Recently, mathematical models have been used to study the transmission dynamics of cholera. For example, Capasso and Paveri-Fontana (1979) formulated a mathematical model to investigate the 1973 cholera epidemic in the European Mediterranean region. Codeco (2001) proposed a susceptible-infected-recovered ($S-I-R$) model for cholera, considering the role of the aquatic reservoir. Johnson (2006) developed a mathematical model for cholera. Wang and Modnak (2011) formulated a mathematical model for cholera to study the effects of vaccination, therapeutic treatment and water sanitation. Sanches *et al;* (2011) developed mathematical models to explore the role of immunity and seasonality in cholera epidemics. Fakai and Ibrahim (2013) proposed a deterministic mathematical model of cholera for predicting chances of outbreak. Modeling cholera disease with education and chlorination can be seen in Al-arydah *et al;* (2013). Samadder (Tapadar) *et al;* (2014) modified the model by Codeco (2001) to study the dynamic behavior of cholera. In this paper, a mathematical model incorporating primary and booster vaccinations as controls is formulated, highlighting the role of booster vaccination.

The model is given as follows.

$$\frac{dS}{dt} = \Delta - \mu S - \frac{\beta(t)VS}{k+V} + \gamma I - \varepsilon S + \alpha S_v \qquad 1.1$$

$$\frac{dS_v}{dt} = p\varepsilon S - (1-\sigma)\frac{\beta(t)VS_v}{k+V} - (\mu + \delta + \alpha)S_v \qquad 1.2$$

$$\frac{dI}{dt} = \frac{\beta(t)VS}{k+V} + (1-\sigma)\frac{\beta(t)VS_v}{k+V} - (\mu + \mu_1 + \gamma)I \quad 1.3$$

$$\frac{dR}{dt} = (1-p)\varepsilon S + \delta S_v - \mu R \quad 1.4$$

$$\frac{dV}{dt} = (m-n)V + eI \quad 1.5$$

Where the variables/parameters are given in Table 1

Table 1

Variable/ parameter	Definition	value	Reference
S(t)	Number of susceptible individuals at time t	$S(0) = 5000$	assumed
$S_v(t)$	Number of individuals partially or not immune after primary	$S_v(0) = 0$	assumed
I(t)	Number of infected individuals at time t	$I(0) = 5$	assumed
R(t)	Number of protected individuals at time t	$R(0) = 0$	assumed
V(t)	Concentration of vibrio cholerae at time t	$V(0) = 10^5$	assumed
Δ	Constant human recruitment rate	0.01	assumed
μ	Human population death rate	5×10^{-5}	Azaele et al (2010)
μ_1	cholera disease − related death rate	5×10^{-3}	assumed
β(t)	contact rate function	0.075	Wang & *Modnak*
γ	rate at which I − individuals become susceptible	0.2	Wang & *modnak*
ε	Rate of primary vaccination	variable	-
$1-\sigma$	proportion of S_v infected after primary vaccination	variable	-
δ	rate at which S_v − individuals are vaccinated and protected	variable	-
α	rate at which the immnuity of S_v − individuals wane	0.01	Alarydah (2013)
e	rate of human contribution to vibrio cholerae	10 cells/ml	Azaele et al (2010)
m	growth rate of V. cholerae	0.022	assumed
n	death rate of V. cholerae	0.033	Azaele et al (2010
k	V. cholerae concentration that yields 50% chance of catching infection	10^6 cells/ml	Wang &*Modnak*(20
p	proportion partially or not immuned after vaccination	0.35	Fung et al (2014)

Equilibrium Analysis

For the special case where the contact rate function is a constant, that is, $\beta(t) = \beta_e$, the model $(1.1 - 15)$ is reduced to an autonomous system as follows.

$$\frac{dS}{dt} = \Delta - \mu S - \frac{\beta_e VS}{k+V} + \gamma I - \varepsilon S + \alpha S_v \quad 1.6$$

$$\frac{dS_v}{dt} = p\varepsilon S - (1-\sigma)\frac{\beta_e VS_v}{k+V} - (\mu + \delta + \alpha)S_v \quad 1.7$$

$$\frac{dI}{dt} = \frac{\beta_e VS}{k+V} + (1-\sigma)\frac{\beta_e VS_v}{k+V} - (\mu+\mu_1+\gamma)I \quad 1.8$$

$$\frac{dR}{dt} = (1-p)\varepsilon S + \delta S_v - \mu R \quad 1.9$$

$$\frac{dV}{dt} = (m-n)V + eI \quad 1.10$$

The Basic Reproduction Number

The disease-free equilibrium state for the model (1.6-1.10) is given by $E_0 = (S_0, S_{v0}, 0, 0)$, where
$S_0 = \frac{p\Delta(\mu+\delta+\alpha)}{\mu(\mu+\delta+\alpha)+\varepsilon(\mu+\delta)}$ and $S_{v0} = \frac{p\varepsilon\Delta}{\mu(\mu+\delta+\alpha)+\varepsilon(\mu+\delta)}$.

For the purpose of analysis, equations (1.6), (1.7), (1.8) *and* (1.10) are used and R can always be expressed as $R = N(t) - \big(S(t) + S_v(t) + I(t)\big)$, $N(t)$*is the total human population at time* t.

For ease of analysis, we do variable transformation as follows.

Let $X = [x_1, x_2, x_3, x_4]^T = [S, S_v, I, V]^T$ so that equations (1.6), (1.7), (1.8) *and* (1.10) can be expressed in the form;

$\frac{dX}{dt} = F = (f_1\ f_2\ f_3\ f_4)$ such that

$$\frac{dx_1}{dt} = \Delta - \mu x_1 - \frac{\beta_e x_1 x_4}{k+x_4} + \gamma x_3 - \varepsilon x_1 + \alpha x_2 \quad (1.11)$$

$$\frac{dx_2}{dt} = p\varepsilon x_1 - (1-\sigma)\frac{\beta_e x_2 x_4}{k+x_4} - (\mu+\delta+\alpha)x_2 \quad (1.12)$$

$$\frac{dx_3}{dt} = \frac{\beta_e x_1 x_4}{k+x_4} + (1-\sigma)\frac{\beta_e x_2 x_4}{k+x_4} - (\mu+\mu_1+\gamma)x_3 \quad (1.13)$$

$$\frac{dx_4}{dt} = (m-n)x_4 + ex_3 \quad (1.14)$$

To compute the basic reproduction number, we use the recipe by Wang and Modnak (2011), Van den Driessche and Watmough (2002), Heffernan (2005) and Ameh (2009). The appearance of new infections is given by the vector

$F(x) = \begin{pmatrix} \frac{\beta_e x_1 x_4}{k+x_4} + (1-\sigma)\frac{\beta_e x_2 x_4}{k+x_4} \\ 0 \end{pmatrix}$ and the vector of other transfer terms is given by

$V(x) = \begin{pmatrix} (\mu+\mu_1+\gamma)x_3 \\ -(m-n)x_4 - ex_3 \end{pmatrix}$.

The matrix of partial derivatives of $F(x)$ is given by

$F_x = \begin{pmatrix} 0 & \beta_e S_0 + (1-\sigma)\beta_e S_v \\ 0 & 0 \end{pmatrix}$ and the matrix of partial derivatives of $V(x)$ is given by

$V_x = \begin{pmatrix} (\mu+\mu_1+\gamma) & 0 \\ -e & -(m-n) \end{pmatrix}$.

The basic reproduction number is given by

$R_0 = F_x V^{-1} = \frac{e[\beta_e S_0 + (1-\sigma)\beta_e S_v]}{(\mu+\mu_1+\gamma)(n-m)}$.

Remark 1: R_0 becomes biologically meaningful if $n > m$.

Local Stability Of The Disease-Free Equilibrium (Dfe)

The Jacobian matrix for the model at the DFE is given by

$$J_{E0} = \begin{pmatrix} -\varepsilon p(\mu+\varepsilon) & \alpha p\varepsilon & p\varepsilon\gamma & p\varepsilon\beta S_0 \\ 0 & \alpha p\varepsilon - (\mu+\delta+\alpha)(\mu+\varepsilon) & p\varepsilon\gamma & -[p\varepsilon\beta S_0 + (1-\sigma)\beta S_v(\mu+\varepsilon)] \\ 0 & 0 & -(\mu+\mu_1+\gamma) & \beta S_0 + (1-\sigma)\beta S_v \\ 0 & 0 & e & m-n \end{pmatrix}$$

Theorem 1: If $R_0 < 1$, then the disease-free equilibrium state E_0 is locally and asymptotically stable.

Proof: To prove theorem 1, it suffices to show that all the eigen values of the characteristic equation for the Jacobian matrix J_{E0} above have negative real parts.

Two of the eigen values of the characteristic equation corresponding to J_{E0} are $\lambda_1 = -\varepsilon(\mu+\varepsilon)$ and $\lambda_2 = \alpha p\varepsilon - (\mu+\delta+\alpha)(\mu+\varepsilon) < 0$. The reduced matrix from J_{E0} is given by

$$A = \begin{pmatrix} -(\mu+\mu_1+\gamma) & \beta S_0 + (1-\sigma)\beta S_v \\ e & m-n \end{pmatrix}.$$

The $Trace(A) = -(\mu+\mu_1+\gamma)(m-n) < 0$ and

$\text{Det}(A) = (\mu+\mu_1+\gamma)(n-m) - e[\beta_e S_0 + (1-\sigma)\beta_e S_v]$

$= (\mu+\mu_1+\gamma)(n-m)\{1 - \frac{e[\beta_e S_0 + (1-\sigma)\beta_e S_v]}{(\mu+\mu_1+\gamma)(n-m)}\}$

$= (\mu+\mu_1+\gamma)(n-m)[1-R_0] > 0$ if $R_0 < 1$.

By this all the eigen values are negative and therefore, the DFE is locally and asymptotically stable if $R_0 < 1$.

Existence and Stability of Endemic Equilibrium (EE)

In this section, we investigate the bifurcation behavior of a general epidemic model around the critical value $R_0 = 1$ in a neighbourhood of a disease-free equilibrium, E_0. Let $\varphi = R_0 - 1$ and rewrite our general epidemic model in the following way:

$$x' = f(x, \varphi) \qquad (1.15)$$

With the assumption that f is continuously differentiable at least twice. We have the following result. Let $D_x f(E_0, 0)$ be the matrix of partial derivatives of f at the disease-free equilibrium. Also let u and v be the right and the left eigenvectors of $D_x f(E_0, 0)$ respectively.

Theorem 2: (Mukandavire *et al;* 2010). Consider the disease transmission model defined by $(1.11 - 1.14)$ with the function $f(x, \varphi)$, φ is the parameter as described from the foregoing. Assume that the zero eigenvalue of $D_x f(E_0, 0)$ is simple. Let

$a = \sum_{k,i,j=1}^{n} v_k u_i v_j \frac{\partial^2 f_k}{\partial_{x_i} \partial x_j}(E_0,0)$, $b = \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial_{x_i} \partial_\phi}(E_0,0)$. Assume that $b \neq 0$. Then, there exists $\delta > 0$ such that

(i) If $a > 0$, $b > 0$, when $\varphi < 0$ with $|\varphi| < 1$, E_0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \varphi < 1$, E_0 is unstable and there exists a negative asymptotically stable equilibrium;

(ii) If $a<0,\ b<0$, when $\varphi<0$ with $|\varphi|<1, E_0$ is unstable; when $0<\varphi<1$, E_0 is asymptotically stable, and there exists a positive unstable equilibrium;

(iii) If $a>0,\ b<0$, when $\varphi<0$ with $|\varphi|<1$ E_0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0<\varphi<1$, E_0 is stable and a positive unstable equilibrium appears

(iv) If $a<0,\ b>0$, when φ changes from negative to positive, E_0 changes its stability from stable to unstable. Corresponding negative equilibrium becomes positive and locally asymptotically stable.

Theorem 2 is applied in the sequel. The left eigenvector for J_{E0} is given by $v=(v_1,v_2,v_3,v_4)^T$, where
$v_1=v_2=0;\ v_3=1, v_4=\frac{(\mu+\mu_1+\gamma)}{e}$. Also, the right eigenvector for J_{E0} is given by $u=(u_1,u_2,u_3,u_4)^T$, where
$v_1=<0; u_2=<0;\ u_3=1, u_4=\frac{(\mu+\mu_1+\gamma)}{e[\beta_e S_0+(1-\sigma)\beta_e S_v]}$.

It is clear from $(1.11-1.14)$ that
$\frac{\partial^2 f_3}{\partial x_1 \partial x_4}=\beta_e;\ \frac{\partial^2 f_3}{\partial x_2 \partial x_4}=(1-\sigma)\beta_e$ and $\frac{\partial^2 f_3}{\partial x_4 \partial \beta_e}=S_0+(1-\sigma)S_{v0}$.
Therefore, $a=v_3u_1u_4\beta_e+v_3u_2u_4(1-\sigma)\beta_e<0$ and $b=v_3u_4[S_0+(1-\sigma)S_{v0}]>0$.

Therefore, by item (iv) of theorem 2, the disease-free equilibrium becomes unstable and the endemic equilibrium becomes locally asymptotically stable as R_0 changes values from less than one to values slightly greater than one.

Seasonal Cycles on Cholera Transmission

Here, we assume that the contact rate function $\beta(t)$ varies sinusoidally and is defined by

$\beta(t) = \beta_0[1 + r_0 \sin(2\pi t/365)]$. For simulation here, $\beta_0 = 0.075$ and $r_0 = 0.3$.

The effects of seasonal cycles on the transmission dynamics of cholera can be seen in Figure 3.

NUMERICAL SIMULATION

The numerical simulations, using fixed published values contained in Table 1 and varying values of control parameters are performed as follows.

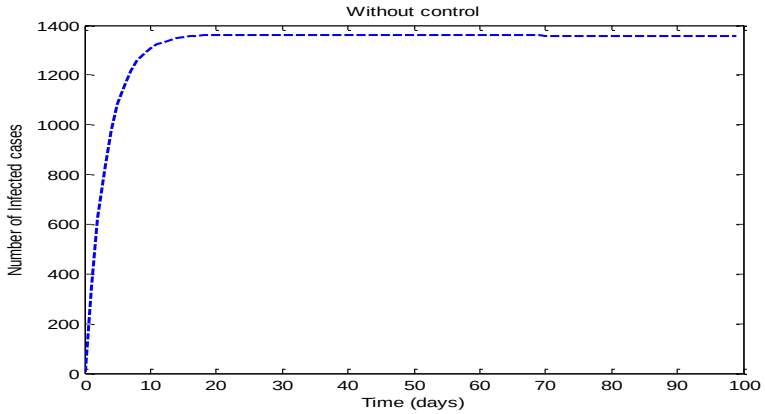

Figure 1: Graph showing the number of infected individuals for the autonomous system; $\varepsilon = 0; \delta = 0$

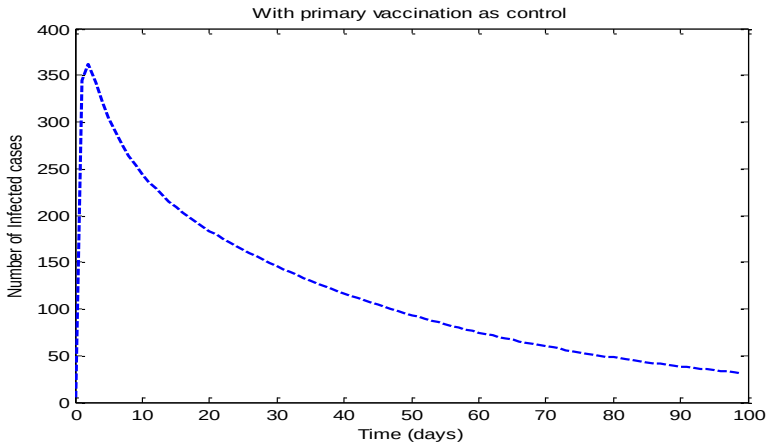

***Figure 2*: Graph showing the number of infected individuals for the autonomous system; $\varepsilon = 0.8; \delta = 0$**

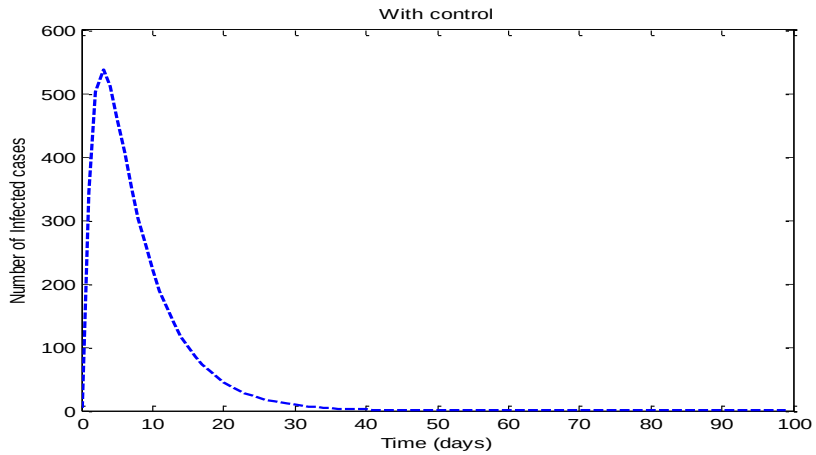

***Figure* 3: Graph showing the number of infected individuals for the autonomous system; $\varepsilon = 0.5; \delta = 0.5$**

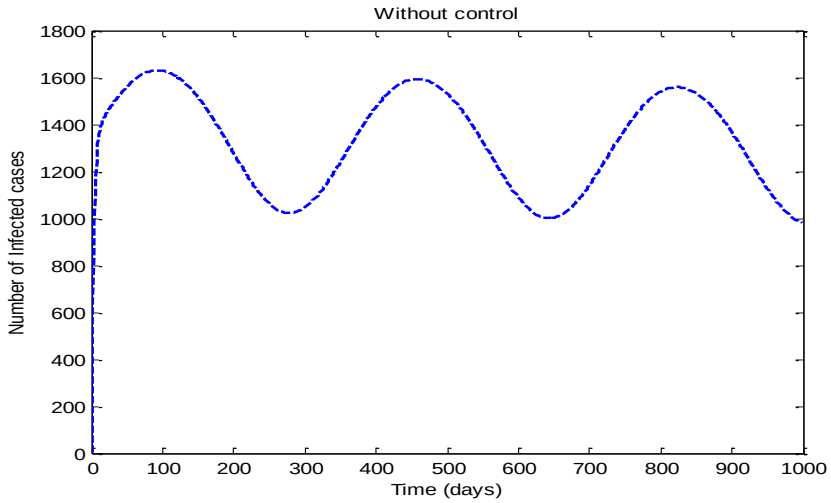

Figure 4: Graph showing the number of infected individuals for the non $-$ autonomous system; $\varepsilon = 0; \delta = 0;\ \beta(t) = 0.075[1 + 0.3\sin(2\pi t/365)]$

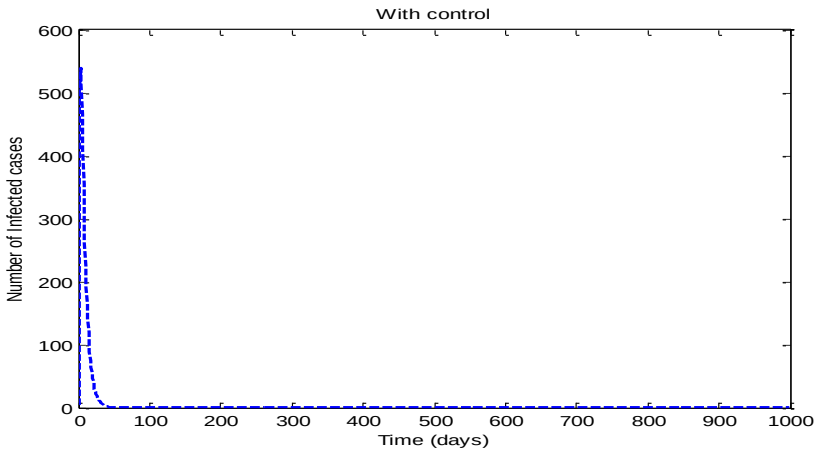

***Figure* 5: Graph showing the number of infected individuals for the non − autonomous system;**
$\varepsilon = 0.5; \delta = 0.5;\ \beta(t) = 0.075[1 + 0.3\sin(2\pi t/365)]$

DISCUSSION

In this paper, a fundamental result is the basic reproduction number for the model. The basic reproduction number is an epidemic threshold that determines the spread of a disease and is therefore, very important for public health policy. The results of equilibrium analysis showed that the disease-free equilibrium state is locally and asymptotically stable for $R_0 < 1$. This result can be seen in theorem 1. This means that cholera disease cannot spread. The results of equilibrium analysis further showed that the endemic equilibrium state is locally and asymptotically stable for$R_0 > 1$. This implies that cholera disease can spread and there could be disease persistence. The result can be found in theorem 2.

The numerical results can be seen in Figures 1 through 5. Figure 1 shows that there is a possibility of an epidemic and disease persistence in absence of control. Figure 2 also shows that primary vaccination alone cannot eradicate the disease from the population.. Figure 3 depicts disease control in the presence of effective primary and booster vaccination programs. Figure 4 shows seasonal variations in the spread of cholera disease when there is a seasonally forced contact rate function in absence of control. These fluctuating epidemics are observed in reality, especially when there is no control. However, Figure 5 shows

that there is control of cholera disease under a seasonally forced transmission parameter when there are effective primary and booster vaccination programs. The findings of this study highlight the benefits of booster vaccination in the control of cholera epidemics.

CONCLUSION

In this research work, a mathematical model for cholera transmission dynamics incorporating primary and booster vaccination parameters as controls formulated and analyzed. The model can be seen in section1. The basic reproduction number was computed by the next generation method. This can be seen in section 2.2. The local stability analysis of the equilibrium states was carried out. The main results can be found in theorems 1 and 2. The effect of a seasonally forced transmission parameter on cholera epidemics was studied. A sinusoidal function is defined in section 2.5. The results of the numerical simulations can be seen in Figures 1 through 5. In this study, it was found out that effective primary and booster vaccination programs are important measures for the control of cholera epidemics.

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