Research Article

Optimal Control and Cost-Effectiveness Analysis of Cholera with Vaccination

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Cholera has been a major global public health problem that is caused due to unsafe water and improper sanitation. These causes have been mainly occurring among the developing country. In this paper, a deterministic model for cholera is formulated with the inclusion of drug resistance compartment. Also, vaccination of newly born babies is considered so as to study its effect on the control. The total population in the present model is divided into five compartments, namely, susceptible, vaccinated newborns, infected, drug resistance, and recovered. The model is mathematically formulated resulting in a system of five ordinary differential equations. In order to verify that the model is valid, it is shown that the solution of the system of equations exists and is both positive and bounded. Fundamental properties of the model such as the basic reproduction number are calculated by employing the method of next-generation matrix. Also, the equilibrium points are identified and their stability analysis is checked. Further in this work, Pontryagin’s maximum principle is employed so as to determine the optimal control strategies of the epidemic. The simulation study has revealed that the application of prevention methods will play a significant role in controlling or minimizing the spread of the disease. From the simulated graphs, we observed that an increment in vaccinated population leads to the reduction of the number of infectious population. Moreover, it is shown that if all the intervention strategies are employed together, then the disease will get eradicated within a short span of time. Also, the analysis of cost-effectiveness is conducted. Finally, the simulated values of optimal controls show that the combination of prevention, education, and treatment of individuals with drug resistance is the most efficient and less costly so as to eradicate disease from the community.

1. Introduction

Cholera is an acute diarrheal illness. It is caused due to infection in both large and small intestines. Such infection occurs due to bacterium *Vibrio cholerae* that lives in an aquatic organism. The consumption of contaminated water and/or food can lead to cholera outbreak, as John Snow showed in 1854 [1]. Also, susceptible individuals are infected whenever they come in contact with infected ones. People live together; shares food and water storage are subjected to propagate the disease among them more quickly [1]. An infected individual can be either symptomatic or asymptotic. Some of the symptoms are watery diarrhea, vomiting, and also leg cramps. If an infected individual is not treated in time then he/she will become dehydrated, suffer with acidosis, collapse, and ultimately lead to death within a day [2]. A recovered individual remains immune to the disease for a period of 3 to 10 years. However, some research results suggest that immunity may last only for some weeks to months [3]. Cholera is still a threat in the places where clean water, sanitation, and hygiene are either poor or absent [4]. In general, 1.3 to 4.0 million cases of cholera occur worldwide per year and of them 21 to 143 thousands will die [5]. Furthermore, about 1.3 billion people are at risk of cholera in endemic countries. So far, large cholera outbreaks occurred in Africa, South Asia, and South East Asia. In 2010, Haiti fought with the world’s largest cholera outbreak ever that infected over 0.6 million leading to 8 thousand deaths [6]. In 2016, Yemen recorded about 0.3 million cholera cases and 1634 associated deaths [7].

According to [8], there has been a significant down-trend in cholera infection though the outbreaks are
happening. In Ethiopia, during 25 April and 6 June 2019, as many as 424 cholera cases and about 15 deaths had been recorded. The most affected region in Ethiopia is Amhara with 198 cases, followed by Oromia with 168 cases, Somali with 33 cases, Addis Ababa with 15 cases, and Tigray with 10 cases. Of these, 13 cases were caused due to cultural activities: 5 in Oromia, 4 in Addis Ababa, 2 in Amhara, and 2 in Tigray.

It is assumed that the strategies like quality water, sanitation, and hygiene will control cholera [4]. However, there have been numerous examples of persistence and significance of cholera in spite of the application of aforementioned control strategies. Therefore, vaccination has been recommended as an additional strategy to control cholera. Now, oral cholera vaccine for new born babies is available and is more effective than early-generation parenteral vaccines. It is very effective to control both endemic and epidemic cholera [9]. Reference [10] formulated an optimal control problem of cholera epidemic model considering education and chlorination as control measures in which they found that education is more effective than chlorination in decreasing bacteria and the number of cholera from the community.

So far, a good number of mathematical models have been developed and analyzed to understand the dynamics of cholera. In [3] a SIR model dividing the human population in to susceptible, infectious, and recovered compartments and dividing bacterial concentrations into hyperinfectious and less infectious compartments has been considered. However, the infectious individuals are further divided into two compartments based on the individuals that are asymptomatic and symptomatic. In [11] with yet another SIR model some control strategies are considered including public health educational campaigns, vaccination, quarantine, and treatment. These strategies have been proved to be very promising and effective in controlling the spread of the disease. Further in [12], SIR-B type model is introduced in which vaccination and disinfection as control measures of cholera are included. In all aforementioned models, it is well proved that the cholera outbreak can be kept under control if both vaccination and treatment are administered effectively in the population. It indicates that, by strengthening both these strategies sufficiently the epidemic can be eliminated from the populations. However, it is true that immigration is a potential factor for the spread of cholera [13].

Considering all the models of the literature as cited here, we improve the work done by [12] by considering the novelty of our work with the inclusion of (i) new born vaccinated individuals, (ii) direct transmission of cholera, (iv) drug resistance individuals, and (v) cost-effectiveness analysis and then we developed a new model of cholera: $VIR,R$ susceptible-vaccinated-infectious-drug resistance-recovered. Further sections of the present paper are organized as follows: In Section 2, a system of five nonlinear ordinary differential equations is formulated to describe the transmission dynamics of cholera. It is shown that the solution for this system exists and is unique. Also, the solutions are proved to be both positive and bounded. Hence, this model is termed as mathematically well posed and biologically meaningful. The basic reproduction number is formulated. Equilibrium including disease-free and endemic are identified and their local and global stabilities are analyzed. In Section 3, optimal control problem is presented and analyzed. In Section 4, numerical simulations are carried out. In Section 5, the analysis of cost-effectiveness is depicted. The paper ends in Section 6, by deriving some conclusions depending on the importance of control variables.

2. Description and Formulation of Modified Model

The developed model divides the entire population into five compartments or classes according to their disease status: Susceptible individuals $S(t)$: these are the individuals that are at risk of infection by cholera disease. Infectious individuals $I(t)$: these individuals are infected; they show symptoms and are also capable of transferring the infection to others. Vaccinated individuals $V(t)$: it consists of new born vaccinated population and they are still acquiring partial immunity against cholera diseases. Drug resistance individuals $R(t)$: Medicines do not work on these infected people. That is, treatment cannot reduce the infection in these people. Recovered individuals $R(t)$: This class includes all the individuals that are recovered from the disease and got temporal immunity. However, a fraction of these people may become susceptible in due course. New population is recruited in to the model with a constant rate of $\Gamma$ per capita. We assume that the new born vaccinated population against cholera with fraction of recruited population $\alpha$ and a fraction $\alpha'$ of the people will go to vaccinated class $V$ and the remaining fraction $(1-\alpha)$ with less immunity will go to susceptible class $S(t)$. Vaccinated population joins susceptible class with per capita rate of $\theta$, as well as from recovered class $R$ with rate $\omega$. Due to the fact that vaccines are not fully immune for cholera epidemic disease, the vaccinated can still become infected again. As a matter of fact, the vaccination against cholera disease does not stop completely being infected but it reduces the probability of being infected. Hence, we assumed the law of mass action interaction between vaccinated and infected compartments [14, 15]. Individuals in the drug resistance class move to recovered class at a per capita rate of $\pi$ by drug efficacy of $\rho$ proportion of individuals who join the recovered class or join the infected class with $(1-\rho)$ proportion by adapting the drug. In all subclasses, $\mu$ is the natural death rate and $\xi$ is the disease-induced death rate. The vaccinated and susceptible individuals become infected with probability $\beta$. The susceptible populations are infected with a rate $\beta R$ and the vaccinated populations are infected with a rate of $\beta R$ for $0 \leq k \leq 1$. If the vaccination protection efficacy is 100% then $\kappa = 0$ and if the vaccination protection effectiveness is 0 then $\kappa$ is equal to one. Here $1-\kappa$ is the reduction in cholera infection risk due to vaccination effectiveness. Also $\phi$ is the rate at which an infected individual leaves the
infectious compartment $I(t)$ and joins the class $R$. The model is based on the $SVIR, RS$ transmission model. The total population size at time $t$ is denoted by $N(t)$, and therefore we have

$$N(t) = S(t) + V(t) + I(t) + R_s(t) + R(t).$$

(1)

2.1. Model Assumptions. When formulating the model, the following assumptions were made:

(i) Here we assume a homogeneous mixing of individuals in the population, which means that each uninfected individual has an equal probability of becoming infected when it comes into adequate contact with infected persons.

(ii) Indirect transmission of cholera through environment to person is negligible, so we consider cholera is transmitted directly from person to person [16].

(iii) Due to waning immunity in the vaccinated host, some of the vaccinated individuals will be susceptible to badger bacteria.

(iv) Due to loss of immunity, we assume that recovered individuals transition to the $\omega$ rate sensitive class.

(v) We also assume that some recruits will emerge in the sensitive class, $S$, at a rate $(1 - \alpha)\Gamma$ and the vaccinated class $V$ at a rate $\alpha\Gamma$.

(vi) The effectiveness of the vaccine is not complete, so some of the vaccinated individuals will be infected with bacteria.

(vii) We also assume that all parameters to be used in this model are positive.

Given the definitions, assumptions, and interrelationships between variables and parameters, the basic dynamics of cholera vaccination for infants is shown in Figure 1.

Based on the model assumption and the schematic diagram the model equation is formulated as follows:

- $\frac{dS(t)}{dt} = (1 - \alpha)\Gamma + \theta V + \omega R - \mu S - \beta rSI,$
- $\frac{dV}{dt} = \alpha\Gamma - \beta krVI - (\theta + \mu)V,$
- $\frac{dI(t)}{dt} = \beta rSI + \beta krVI + (1 - \rho)\pi R_s - (\gamma + \phi + \mu + \xi)I,$
- $\frac{dR_s(t)}{dt} = \gamma I - (\pi + \mu)R_s,$
- $\frac{dR(t)}{dt} = \rho \pi R_s + \phi I - (\omega + \mu)R.$

(2)

It goes along the initial conditions (ICs)

$$S(0) = S_0 \geq 0,$$
$$V(0) = V_0 \geq 0,$$
$$I(0) = I_0 > 0,$$
$$R_s(0) = R_s_0 > 0,$$
$$R(0) = R_0 > 0.$$  

(3)

2.2. Invariant Region. In this subsection, we obtain a region in which the solution of (2) is bounded.

Theorem 1. The feasible solution set $S, V, I, R_s, R$ of the system equation of the model entered and bounded in the region:

$$\Omega = \left\{ (S, V, I, R_s, R) \in \mathbb{R}_+^5; \quad 0 \leq N \leq \frac{\Gamma}{\mu} \right\}.$$  

(4)

Proof. Here, in this section, the invariant region in which the solutions of the system of equations given in (2) are bounded will be obtained. Now, on differentiating the total population $N(t) = S(t) + V(t) + I(t) + R_s(t) + R(t)$ with respect to time $t$ and substituting into equation (2), the simplified equation can be obtained as

$$\frac{dN}{dt} = \Gamma \mu N - \xi I.$$  

(5)

Initially either there is no infection or it is negligible $I \geq 0$ and also the disease-induced death rate satisfies $\xi \geq 0$. Thus, without loss of generality (5) can be reexpressed as $dN/dt \leq \Gamma \mu N$ which on solving using separation of variables method gives

$$N \leq \frac{\Gamma}{\mu} \left( \frac{\mu N_0}{\xi} \right) e^{-\mu t}.$$  

(6)

Further, it can be observed that $N(t) \to (\Gamma/\mu)$ as $t \to \infty$. That is, the total population $N(t)$ takes off from the value $N(0)$ at the initial time $t = 0$ and ends up with the bounded value $(\Gamma/\mu)$ as the time $t$ grows to infinity. Thus, it can be concluded that $N(t)$ is bounded as $0 \leq N(t) \leq (\Gamma/\mu)$. Thus, the feasible solution set of the system equation of the model enters and remains in the region.

Further, it can be observed that $N(t) \to (\Gamma/\mu)$ as $t \to \infty$. That is, the total population $N(t)$ takes off from the initial value $N(0)$ at the beginning and ends up with the bounded value $(\Gamma/\mu)$ as time grows to finitely large. Thus, it can be concluded that $N(t)$ is bounded; i.e., $0 \leq N(t) \leq (\Gamma/\mu)$. Thus, the solution set of the system of model (2) enters and remains in the feasible region:

$$\Omega = \left\{ (S, V, I, R_s, R) \in \mathbb{R}_+^5; \quad 0 \leq N \leq \frac{\Gamma}{\mu} \right\}.$$  

(7)
Therefore, the system of model (2) is biologically well-posed and mathematically meaningful. Hence, it is appropriate and sufficient to study the dynamics of the model variables in the invariant region $\Omega$.

2.3. Positivity of the Solution. The solution of the system remains positive at any point in time $t$, if the initial values of all the variables are positive.

**Theorem 2.** Let the initial data be $(S(0), V(0), I(0), R_s(0), R(0)) > 0 \in \Omega$. Then, the solution set $S(t), V(t), I(t), R_s(t), R(t)$ of system (2) is positive for all $t \geq 0$.

**Proof.** From the third equation of model system (2):

$$\frac{ds}{dt} = (1 - \alpha)I + \theta V + \omega R - \mu S - \beta r SI,$$

$$\frac{ds}{dt} \geq - (\beta r I + \mu)S,$$

$$\frac{ds}{dt} \geq - (\beta r I + \mu)dt.$$  

Now, by using separation of variables method and applying on integration, solution of foregoing differential inequality is found as

$$S(t) \geq S_0 e^{-(\beta r I + \mu)dt} \geq 0.$$  

Hence it can conclude that $S(t) \geq 0$.

Similarly, we obtained

$$V(t) \geq V_0 e^{-(\beta + \theta + \mu + \xi)dt} \geq 0,$$

$$I(t) \geq I_0 e^{-(\gamma + \phi + \mu + \xi)dt} \geq 0,$$

$$R_s(t) \geq R_{s0} e^{-(\mu + \xi)dt} \geq 0,$$

$$R(t) \geq R_{0} e^{-(\omega + \mu)dt} \geq 0.$$  

Thus, it can be shown that the model equations of system (2) are positive for all $t \geq 0$. Hence, the model is meaning full and well posed in $\Omega$.

2.4. The Disease-Free Equilibrium (DFE). In order to find the disease-free equilibrium (DFE) point of the model, the right hand sides of the system of equations given in (2) are equated to zero, evaluating the resultant equations at $I = R_s = R = 0$ and solving for noninfected state variables. Thus, disease-free equilibrium is identified as

$$E_0 = (S^0, V^0, I^0, R_s^0, R^0) = \left(\frac{(\mu + \theta - \mu \alpha)\Gamma}{\mu (\theta + \mu)}, \frac{\alpha \Gamma}{\theta + \mu}, 0, 0, 0, 0\right).$$  

2.5. The Basic Reproduction Number $R_0$. Here, the threshold parameter that governs the spread of disease known as the basic reproduction number is obtained. It is nothing but the spectral radius of the next-generation matrix. For the purpose, the system of model (2) is rearranged starting with those representing newly infective classes [17].

$$\frac{dI(t)}{dt} = \beta r SI + \beta \kappa T V I + (1 - \rho) \pi R_s - (\gamma + \phi + \mu + \xi)I,$$

$$\frac{dR_s(t)}{dt} = \gamma I - (\sigma + \mu)R_s.$$  

Then by the principle of next-generation matrix, we obtained

$$f_i = \begin{bmatrix} \beta r SI + \beta \kappa T V I \\ 0 \\ h v_1 - (1 - \rho) \pi R_s \\ h \phi R_s - \gamma I \end{bmatrix},$$

$$v_i = \begin{bmatrix} h \phi R_s - \gamma I \end{bmatrix}.$$  

![Figure 1: Schematic diagram of model equation.](image-url)
Now partially differentiating the variables $I$ and $R_S$ with respect to time and evaluating at the disease-free equilibrium point reduces the Jacobian matrices to

$$
F = \begin{bmatrix}
(h_1 - \mu \alpha)\beta r_1 + \mu \alpha^2 r_1 & \mu h_1 \\
0 & 0
\end{bmatrix},
$$

$$
V = \begin{bmatrix}
h_2 & -(1 - \rho)\pi \\
\gamma & h_3
\end{bmatrix},
$$

$$
V^{-1} = \begin{bmatrix}
h_3 & (1 - \rho)\pi \\
\gamma & h_2
\end{bmatrix}.
$$

Thus, the basic reproduction number, $R_0 = \lambda(FV^{-1})$, where $\lambda$ is the largest eigenvalue of the product $FV^{-1}$ and $R_0$ at disease-free equilibrium point is as follows:

$$
R_0 = \frac{h_1[(h_1 - \mu \alpha)\beta r_1 + \mu \alpha^2 r_1]}{\mu h_1}.
$$

Det $(V) = h_1h_3 - (1 - \rho)\gamma\pi h_1 = \theta + \mu, h_2 = \gamma + \phi + \mu + \xi.

h_3 = \pi + \mu,

h_4 = \omega + \mu.

2.6. Local Stability of Disease-Free Equilibrium

**Theorem 3.** Disease-free equilibrium $E_0$ of system of equations given in (2) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

**Proof.** Now, the Jacobian matrix of the model equations given in (2) at the disease-free equilibrium $E_0$ reduces the form as follows:

$$
J(E_0) = \begin{bmatrix}
-\mu & \frac{-\beta r(h_1 - \mu \alpha)\Gamma}{\mu h_1} & 0 & 0 \\
n_1 & \frac{-\kappa r_1 \alpha \Gamma}{h_1} & 0 & 0 \\
0 & 0 & \left[\frac{\beta r(h_1 - \mu \alpha)\Gamma}{\mu h_1} + \frac{\kappa r_1 \alpha \Gamma}{h_1} - h_2\right] & (1 - \rho)\pi \\
0 & 0 & \gamma & -h_3 \\
0 & 0 & \phi & \rho \pi - h_4
\end{bmatrix}.
$$

From the Jacobian matrix of (17), we obtained a characteristic polynomial:

$$
(-\mu - \lambda)(-h_1 - \lambda)(-h_4 - \lambda) = 0
$$

$$
\begin{bmatrix}
\frac{\beta r(h_1 - \mu \alpha)\Gamma}{\mu h_1} + \frac{\kappa r_1 \alpha \Gamma}{h_1} - h_2 \\
(1 - \rho)\pi \\
\gamma \\
-h_3 - \lambda
\end{bmatrix} = 0,
$$

$$
\Rightarrow[(-\mu - \lambda)(-h_1 - \lambda)(-h_4 - \lambda)][\lambda^2 + a\lambda + b] = 0.
$$

Clearly we see that from (18) the first three eigenvalues are $\lambda = -\mu, \lambda = -h_1, \lambda = -h_4$ which are negative and the remaining eigenvalues are determined using Routh-Hurwitz criteria such that

$$
a = \frac{(\mu h_1 h_2 + \mu h_1 h_3 - \beta r(h_1 - \mu \alpha)\Gamma - \mu \kappa r_1 \alpha \Gamma)}{\mu h_1},
$$

$> 0$ means that, $\mu h_1 h_2 + \mu h_1 h_3 - \beta r(h_1 - \mu \alpha)\Gamma - \mu \kappa r_1 \alpha \Gamma$, and $b = (h_2 h_3 - \gamma(1 - \rho)\pi)[1 - R_0] > 0$ strictly negative real root if and only if $R_0 < 1$ hold.

Thus, the disease-free equilibrium point $(E_0)$ is locally asymptotically stable if $R_0 < 1$.

2.7. Global Stability of Disease-Free Equilibrium

The implementation of global stability of disease-free equilibrium is used by [18] technique. Model (2) can be rewritten as
\[
\begin{align*}
\frac{dX}{dt} &= F(X, Z), \\
\frac{dZ}{dt} &= H(X, Z), \\
H(X, 0) &= 0.
\end{align*}
\]

\(X\) stands for the uninfected population, that is, \(X = (S, V, R)\), and \(Z\) also stands for the infected population, that is, \(Z = (I, R_s)\). The disease-free equilibrium point of the model is denoted by \(V = (X^*, 0)\). The point \(V = (X^*, 0)\) to be globally asymptotically stable equilibrium provided that \(\mathcal{R}_0 < 1\) and the following conditions must be met:

(1) For \(dX/dt = F(X, 0)\), \(X^*\) is globally asymptotically stable.

(2) \(G(X, Z) = AZ - \bar{H}(X, Z), \bar{H}(X, Z), \geq 0\)

\(A = HZG(X^*, 0)\) is a Metzler matrix (the off-diagonal elements of \(A\) are nonnegative and \(H\) is the region where the model makes biological sense). If system (2) met the above two criteria, then the following theorem holds.

**Theorem 4.** The point \(V = (X^*, 0)\) is globally asymptotically stable equilibrium provided that \(\mathcal{R}_0 < 1\) and conditions (2) and (5) are satisfied.

**Proof.** From system (1) we can get \(F(X, Z)\) and \(H(X, Z)\).

Consider the reduced system:

\[
\begin{align*}
\frac{dX}{dt} &= \begin{bmatrix} (1 - \alpha)I + VV + \omega R - \mu S - \beta \tau SI \end{bmatrix} \\
&\quad + \begin{bmatrix} \alpha \tau - (\theta + \mu) V \\
&\quad - (\omega + \mu) \end{bmatrix} + \begin{bmatrix} (\mu + \theta - \mu) \Gamma/\mu + (\theta + \mu) \end{bmatrix} + \begin{bmatrix} [S(0) - ((\mu + \theta - \mu) + (V(0) - (\alpha I)/\theta + \mu))] e^{-\mu t} \end{bmatrix}
\end{align*}
\]

From (22) it is obvious that \(X^* = \{(\mu + \theta - \mu) \Gamma/\mu + (\theta + \mu), \alpha \tau - (\theta + \mu)\} \) is the global asymptotic point. This can be verified from the solution, namely, \(S = ((\mu + \theta - \mu) \Gamma/\mu + (\theta + \mu)) + [S(0) - ((\mu + \theta - \mu) + (V(0) - (\alpha I)/\theta + \mu))] e^{-\mu t}\). As \(t \to \infty\) the solution \(S = ((\mu + \theta - \mu) \Gamma/\mu + (\theta + \mu))\) and \(V = (\alpha I)/\theta + \mu)\) imply the global convergence of (8) in \(\Omega\).

From the equation for infected compartments in the model we have

\[
A = \begin{bmatrix}
(\mu + \theta - \mu) \beta \tau \Gamma + \frac{\beta \tau x \Gamma}{(\theta + \mu)} - h_2
& 1 - \rho
\end{bmatrix}
\]

(23)

Since \(A\) is Metzler matrix, i.e., all off-diagonal elements are nonnegative, then, \(H(X, Z)\) can be written as \(H(X, Z) = AZ - \bar{G}(X, Z)\), where

\[
\bar{H}(X, Z) = \begin{bmatrix}
\bar{H}_1(X, Z) \\
\bar{H}_2(X, Z) \\
\bar{H}_3(X, Z)
\end{bmatrix} = \begin{bmatrix} 0 \\
0 \\
0
\end{bmatrix}.
\]

(24)

It follows that \(\bar{H}_1(X, Z) = \bar{H}_2(X, Z) = \bar{H}_3(X, Z) = 0\). Thus conditions (2) and (5) are satisfied and we conclude that \(E_0\) is globally asymptotically stable for \(\mathcal{R}_0 < 1\). 

2.8. Endemic Equilibrium Points. In this section, we investigate the endemic equilibrium of the diseases which is denoted by \(E^* = (S^*, V^*, I^*, R_s^*, R^*)\) and the interesting idea behind the endemic equilibrium is that it occurs whenever the cholera disease persists in the population. It can be obtained by equating the system of (1) to zero. Thus the reduced form of system (2) will become

\[
\begin{align*}
0 &= (1 - \alpha)I + \theta V + \omega R - \mu S - \beta \tau SI, \\
0 &= \alpha \tau - \beta \tau x V - (\theta + \mu) V, \\
0 &= \beta \tau SI + \beta \tau x V + (1 - \rho) \pi R_s - (\gamma + \phi + \mu + \xi) I, \\
0 &= \gamma I - (\pi + \mu) R_s, \\
0 &= \rho \pi R_s + \phi I - (\omega + \mu) R.
\end{align*}
\]

Hence, after a tiresome solving the resultant of endemic equilibrium \(E^*\) from (9) is given by

\[
\begin{align*}
S^* &= \frac{k_1 k_3}{k_2 k_4 - k_3 k_1}, \\
V^* &= \frac{h_2 (1 - \rho) \gamma \pi k_1 k_3 + \gamma k_2 k_3}{(k_1 k_3 - k_2 k_4) \gamma k_4}, \\
I^* &= \frac{k_1 k_3}{(k_1 k_3 - k_2 k_4) \gamma}, \\
R_s^* &= \frac{k_1 k_3}{(k_1 k_3 - k_2 k_4)}, \\
R^* &= \frac{(\gamma \pi + \phi h_3) k_1 k_3}{\gamma h_4 (k_1 k_3 - k_2 k_4)}.
\end{align*}
\]
\[ \lambda = \beta k_1, k_3 = \gamma h_3 (\lambda k + h_1) (1 - \alpha) + \gamma h_i \theta a \Gamma \\
k_i = \gamma_c \lambda a + \gamma(\lambda k + h_1), k_4 = \gamma h_i h_3 (\mu + \lambda) \\
k_2 = (\lambda k + h_1) \left( [k_2 h_3 - (1 - \rho) \gamma \pi], k_5 \right) = \omega (\lambda k + h_1) (\gamma \rho \pi + \phi h_3) . \]

**Lemma 1.** If \( R_0 > 1 \), then a unique endemic equilibrium point \( E^* \) exists; otherwise, there is no endemic equilibrium.

*Proof.* From equation one of infective class, we have

\[
\begin{align*}
\frac{dI(t)}{dt} &= \beta r S I + \beta k_1 V I + (1 - \rho) \pi R_S - (\gamma + \phi + \mu + \xi) I, \\
\frac{dR_S(t)}{dt} &= \gamma I - (\pi + \mu) R_S.
\end{align*}
\]

(27)

From the first inequality of (28), we obtain

\[ I < \frac{\beta r S I + \beta k_1 V I + (1 - \rho) \pi R_S}{(\gamma + \phi + \mu + \xi) I}, \]

(29)

\[ \Rightarrow I < \frac{\beta r I (S + \kappa V)}{(\gamma + \phi + \mu + \xi) I}. \]

From the second inequality of (28), also we obtain

\[ (\pi + \mu) R_S < \gamma I, \]

(30)

\[ \Rightarrow R_S < \frac{\gamma I}{(\pi + \mu)}. \]

By substituting into (30) and (29) and simplifying, it becomes

\[ I < \frac{[\beta r (\pi + \mu) + (1 - \rho) \pi \gamma] I}{(\pi + \mu) (\gamma + \phi + \mu + \xi) I}. \]

(31)

Then, by substituting and canceling of \( I \) in both sides of (31), we can get

\[ 1 < \frac{[\beta r (\pi + \mu) + (1 - \rho) \pi \gamma]}{(\pi + \mu) (\gamma + \phi + \mu + \xi)} \]

(32)

\[ \Rightarrow 1 < \frac{h_3 [([h_1 - \mu] \beta r \gamma + \mu \alpha \beta \kappa \gamma \xi)]}{h_3 \mu h_1} = R_0. \]

Therefore, a unique endemic equilibrium exists when \( R_0 > 1 \) if and only if \( k_1 k_2 > k_2 k_4 \). \( \square \)

### 3. Extension of the Model into an Optimal Control

This section is dedicated to find the optimal control strategies of the model [19, 20]. This helps to identify the best intervention strategies in order to eradicate the disease within a specified time. These control strategies are education campaign, treatment of individuals with infected human, and treatment of individuals with drug resistance human \( u_1, u_2, \) and \( u_3 \) respectively. After incorporating \( u_1, u_2, \) and \( u_3 \) in (2), optimal control model of cholera is obtained as follows:

\[
\begin{align*}
\frac{dS(t)}{dt} &= (1 - \alpha) \Gamma + \theta V + \omega R - (1 - u_1) \beta r S I - \mu S, \\
\frac{dV(t)}{dt} &= \alpha \Gamma - (1 - u_1) \beta k_1 V I - (\theta + \mu) V, \\
\frac{dI(t)}{dt} &= (1 - u_1) \beta s V I + (1 - u_1) \beta k_1 V I + (1 - u_1) (1 - \rho) \pi R_S - u_2 \phi I - (\gamma + \phi + \mu + \xi) I, \\
\frac{dR_S(t)}{dt} &= \gamma I - (1 - u_1) (1 - \rho) \pi R_S - u_5 \pi R_S - \mu R_S, \\
\frac{dR(t)}{dt} &= u_3 \rho \pi R_S + u_2 \phi I - \mu R.
\end{align*}
\]

(33)

Now, the optimal levels of the control set \( U \) are Lebesgue measurable and it is defined as the control set \( U \) defined as

\[ U = [u_1(t), u_2(t), u_3(t); 0 \leq u_1, u_2, u_3 < 1, \ 0 \leq t \leq T]. \]

(34)

Here, our main objective is to find the associated state variables and the optimal levels of the controls that optimize the objective function \( J \). The method of the objective function is taken from [21] and given by

\[ J = \min_{u_1, u_2, u_3} \int_0^T \left( b_1 I + b_2 R_S + \frac{1}{2} \sum_{i=1}^3 w_i u_i^2 \right) dt. \]

(35)

The coefficients associated with state variables \( b_1 \) and \( b_2 \) and with controls \( (u_i) \) are positive. Due to the fact that cost
is not linear in its condition we make the cost expression 
\((1/2)w_iu_i^2\) quadratic. As objective functional (35) our goal
is to minimize the number of infected and drug resistance
individuals as well as the cost of interventions with control
strategies. Thus, it is sought to find an optimal triple control
\((u_1^*, u_2^*, u_3^*)\) such that
\[
J(u_1^*, u_2^*, u_3^*) = \min\{J(u_1, u_2, u_3); \quad u_i \in U\}. \quad (36)
\]
\(U = \{(u_1, u_2, u_3)\) for each \(u_i\) measurable with \(0 \leq u_i \leq 1\)
for \(0 \leq t \leq t_f\) for the control.

3.1. Existence of an Optimal Control. The necessary condition
for optimal solution is guaranteed under [20]. The existence
of an optimal control can be showed by the result in [22]. The
system of (1) is bounded by a linear system for a finite time
interval; the detail of the proof is given in [23].

(i) The control sets and corresponding state variables
are nonempty

(ii) The control set \(U\) is convex and closed

(iii) The RHS of system (2) is bounded by the linear
function in the state and control

(iv) The integrand of the objective functional is concave
on \(U\)

(v) The function is bounded below by \(m_1−m_2−m_3\)
\((u_1^*, u_2^*, u_3^*)^{\beta/2}\) where \(m_1 > 0, m_2 > 0,\) and \(\beta > 0\)

The existence of the result in (31) for the equation of
system (2) with bounded coefficients is used to hold the
condition under (5). The control set \(U\) is convex and
is closed by definition. The RHS of the state variables in (2)
holds. Condition (6) as the state solutions is a priori
bounded.

\[
\begin{align*}
\frac{d\lambda_1}{dr} &= (\lambda_1 - \lambda_2)(1 - u_1)\beta rI + \lambda_1 \theta, \\
\frac{d\lambda_2}{dr} &= (\lambda_2 - \lambda_3)(1 - u_1)\beta sI + \lambda_2 - \lambda_1 \theta, \\
\frac{d\lambda_3}{dr} &= -b_1(\lambda_1 - \lambda_2)(1 - u_1)\beta rS + \lambda_2(1 - u_1)\beta sV - (\lambda_2 - \lambda_3)(1 - u_1)\beta sV - (\lambda_5 - \lambda_3)u_3\rho + \lambda_3 \phi, \\
\frac{d\lambda_4}{dr} &= -b_2(\lambda_4 - \lambda_5)u_3\rho - \lambda_4 \mu, \\
\frac{d\lambda_5}{dr} &= \lambda_1 \omega.
\end{align*}
\]

Together with the transversality conditions, \(\lambda_i(t_f) = 0,\)
\(i = 1, \ldots, 5.\) Moreover, the optimal controls \(u_1, u_2,\) and \(u_3\) are
given as follows:

The integrand of the objective functional \(b_1I + b_2R_s + \)
\((1/2)\sum_{i=1}^{3} w_iu_i^2\) is clearly concave on \(U.\) Finally, \(m_1 > 0,\)
\(m_2 > 0,\) and \(\beta > 0\) holding
\[
b_1I + b_2R_s + \frac{1}{2} \sum_{i=1}^{3} w_iu_i^2 \leq m_2 - m_1(u_1^*, u_2^*, u_3^*)^{\beta/2}.
\quad (37)
\]
The state variables are bounded. Hence, there exists an
optimal control \((u_1^*, u_2^*, u_3^*)\) that minimizes the objective
functional \(J(u_1, u_2, u_3).\)

3.2. Hamiltonian and Optimality Condition. The necessary
condition for the optimal triple is obtained using the
principle in [20]. Thus, the Hamiltonian (H) is defined by
the following equation:
\[
H = \frac{df}{dr} + \lambda_1 \frac{dS}{dr} + \lambda_2 \frac{dV}{dr} + \lambda_3 \frac{dI}{dr} + \lambda_4 \frac{dR_s}{dr} + \lambda_5 \frac{dR}{dr}
\]
That is,
\[
H(S, V, I, R_s, R) = L(I, R_s, u_1, u_2, u_3) + \lambda_1 \frac{dS}{dt} + \lambda_2 \frac{dV}{dt} + \lambda_3 \frac{dI}{dt} + \lambda_4 \frac{dR_s}{dt} + \lambda_5 \frac{dR}{dt}.
\quad (39)
\]
\(L(I, R_s, u_1, u_2, u_3) = b_1I + b_2R_s + (1/2)\sum_{i=1}^{3} w_iu_i^2\) and \(\lambda_1, \lambda_2,\)
\(\lambda_3, \lambda_4,\) and \(\lambda_5\) are the adjoint variable functions. To obtain
the adjoint variables we followed the classical result of [20].

Theorem 5. Given an optimal control \((u_1, u_2, u_3)\) and
the corresponding state solution \(S, V, I, R_s, R\) of corresponding
system on (14) which minimize the objective function
\(J(u_1, u_2, u_3)\) over \(U\), there exist adjoint variables
\(\lambda_i, i = 1, \ldots, 5\) satisfying the following equations:
\[ u_1^* = \min \left\{ 1, \max \left\{ 0, \frac{(\lambda_3 - \lambda_1) \beta r S^* I^* + (\lambda_3 - \lambda_2) \beta k r V^* I^* + (\lambda_3 - \lambda_4) (1 - \rho) \pi R_s^*}{w_1} \right\} \right\}, \]
\[ u_2^* = \min \left\{ 1, \max \left\{ 0, \frac{(\lambda_3 - \lambda_4) \phi I^*}{w_2} \right\} \right\}, \]
\[ u_3^* = \min \left\{ 1, \max \left\{ 0, \frac{(\lambda_4 - \lambda_3) \pi R_s^*}{w_3} \right\} \right\}. \] (41)

**Proof.** Adjoint equations as well as transversality conditions are obtained from Pontryagin’s maximum principle, such that

\[
\begin{align*}
\frac{d\lambda_1}{dt} &= -\frac{\partial H}{ds} (\lambda_1 - \lambda_3) (1 - u_1) \beta r I + \lambda_1 \theta, \\
\frac{d\lambda_2}{dt} &= -\frac{\partial H}{d\tau} (\lambda_2 - \lambda_3) (1 - u_1) \beta k r I + \lambda_2 (\theta + \mu) - \lambda_1 \theta, \\
\frac{d\lambda_3}{dt} &= -\frac{\partial H}{dR} - b_1 (\lambda_1 - \lambda_3) (1 - u_1) \beta r S + \lambda_2 (1 - u_1) \beta k r V - (\lambda_2 - \lambda_3) (1 - u_1) \beta k r V - (\lambda_5 - \lambda_3) u_3 \phi + \lambda_4 y, \\
\frac{d\lambda_4}{dt} &= -\frac{\partial H}{d\rho} - b_2 (\lambda_4 - \lambda_5) u_3 \psi - \lambda_4 \mu, \\
\frac{d\lambda_5}{dt} &= -\frac{\partial H}{d\omega} - \lambda_5. 
\end{align*}
\] (42)

Again the optimal controls \( u_1, u_2, \) and \( u_3 \) can be solved from the optimality conditions using the method in [20]; we obtain

\[
\frac{\partial H}{du_1} = 0, \text{ i.e. } u_1 = (\lambda_3 - \lambda_1) \beta r S I + (\lambda_3 - \lambda_2) \beta k r V I + (\lambda_3 - \lambda_4) (1 - \rho) \pi R_s,
\]

\[
\Rightarrow u_1 = \frac{(\lambda_3 - \lambda_1) \beta r S I + (\lambda_3 - \lambda_2) \beta k r V I + (\lambda_3 - \lambda_4) (1 - \rho) \pi R_s}{w_1}. \] (43)

By applying the same method for \( u_2 \) and \( u_3 \), we found

\[
u_2 = \frac{(\lambda_3 - \lambda_3) \phi I}{w_2}, \quad u_3 = \frac{(\lambda_4 - \lambda_3) \pi R_s}{w_3}. \] (44)

Putting \( u_1 = u_1^*, u_2 = u_2^*, \) and \( u_3 = u_3^* \) and \( S = S^*, V = V^*, I = I^*, R_s = R_s^* \), we get

\[
\begin{align*}
u_1^* &= \frac{(\lambda_3 - \lambda_1) \beta r S^* I^* + (\lambda_3 - \lambda_2) \beta k r V^* I^* + (\lambda_3 - \lambda_4) (1 - \rho) \pi R_s^*}{w_1}, \\
u_2^* &= \frac{(\lambda_3 - \lambda_3) \phi I^*}{w_2}, \\
u_3^* &= \frac{(\lambda_4 - \lambda_3) \pi R_s^*}{w_3}. \] (45)
The bounds of $u_1, u_2,$ and $u_3$ are $0 \leq u_1, u_2, u_3 < 1$. Hence, optimum control has the following form:

$$u_1^* = \begin{cases} \frac{(\lambda_3 - \lambda_1)\beta r S^* I^*}{w_1}, & \text{if } 0 < u_1^* < 0, \\ 0, & \text{if } u_1^* < 0, \\ 1, & \text{if } u_1^* < 1, \end{cases}$$

$$u_2^* = \begin{cases} \frac{(\lambda_3 - \lambda_2)\phi I^*}{w_2}, & \text{if } 0 < u_2^* < 0, \\ 0, & \text{if } u_2^* < 0, \\ 1, & \text{if } u_2^* < 1, \end{cases}$$

$$u_3^* = \begin{cases} \frac{(\lambda_4 - \lambda_3)\pi R^*}{w_3}, & \text{if } 0 < u_3^* < 0, \\ 0, & \text{if } u_3^* < 0, \\ 1, & \text{if } u_3^* < 1. \end{cases}$$

\[(46)\]

4. Numerical Simulation

The numerical simulations were carried out using the parametric values given in Table 1. Optimality of the system is achieved by using available iterative schemes. Solutions of the state equations given in (2) are initiated by assigning guessed values for the controls and simulated using fourth-order Runge-Kutta scheme. It is followed by using current iterated solutions of the state equations to solve the adjoint equations by backward fourth-order Runge-Kutta scheme.

4.1. Control with Education Alone. Here, optimality system is simulated by incorporating education intervention alone. Figure 2 shows a decrease of infectious and drug resistance populations within a specified time period. Therefore, it is concluded that the education intervention strategy plays an important role in reducing cholera infection in the population.

4.2. Control with Treatment of Infected Population Alone. Here, treatment of infectious population is used as the only intervention strategy. Figure 3 shows that the number of infective together with the drug resistance humans goes down within the specified time period. Hence, this strategy also works well in eradicating the disease from community.

4.3. Control with Treatment of Drug Resistance Population Alone. Here, treatment alone is applied to drug resistance population as an intervention strategy. That is, treating of drug resistance individuals whose medicines do not work on these infected people is considered. In Figure 4, it is observed that the numbers of both infectious and drug resistance populations are decreased whenever treatment intervention is applied. However, the numbers of infectious or drug resistance do not go to zero since the susceptible individuals still get infected as they do not follow any prevention strategies. Therefore, it is concluded that application of optimized treatment of drug resistance population alone as control intervention strategy decreases the burden of the disease. However, it alone cannot eradicate cholera disease completely from the community.

4.4. Control with Education and Treatment of Infectious Population Strategies. Here, the model equations are simulated using a combination of education and treatment of infectious population as intervention strategies for controlling cholera disease in the community. Figure 5 clearly shows that both the infectious and drug resistance populations have gone to zero by end of the implementation period. Therefore, it is concluded that both these strategies are effective in eradicating the disease from the community within a specified period of time.

4.5. Control with Education and Treatment of Drug Resistance Population Strategies. Here, education and treatment of drug resistance population are used as intervention strategies. Figure 6 shows that the number of infectious as well as
Table 1: Parameter values for cholera model.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Γ</td>
<td>20</td>
<td>Assumed</td>
</tr>
<tr>
<td>α</td>
<td>0.085</td>
<td>Assumed</td>
</tr>
<tr>
<td>β</td>
<td>0.02143</td>
<td>Assumed</td>
</tr>
<tr>
<td>θ</td>
<td>0.005</td>
<td>[24]</td>
</tr>
<tr>
<td>ω</td>
<td>0.065</td>
<td>Assumed</td>
</tr>
<tr>
<td>τ</td>
<td>0.73</td>
<td>[24]</td>
</tr>
<tr>
<td>π</td>
<td>0.003</td>
<td>Assumed</td>
</tr>
<tr>
<td>ρ</td>
<td>0.194</td>
<td>Assumed</td>
</tr>
<tr>
<td>κ</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>φ</td>
<td>0.2</td>
<td>[24]</td>
</tr>
<tr>
<td>γ</td>
<td>0.005</td>
<td>Assumed</td>
</tr>
<tr>
<td>μ</td>
<td>0.548</td>
<td>[24]</td>
</tr>
<tr>
<td>ξ</td>
<td>0.015</td>
<td>[24]</td>
</tr>
</tbody>
</table>

Figure 2: Impact of education on infectious and drug resistance populations.

Figure 3: Impact of treatment of infectious on drug resistance and infectious populations.
Figure 4: Impact of treatment of drug resistance on infectious and drug resistance populations.

Figure 5: Impact of education and treatment of infectious population on infectious and drug resistance populations.

Figure 6: Impact of education and treatment of drug resistance population on infectious and drug resistance populations.
drug resistance population reduces considerably to minimum in the specified time period. Therefore, these strategies too work effectively in eradicating the disease from human population.

4.6. Control with Treatment of Infectious and Drug Resistance Population Strategies. Here, treatments of infectious and drug resistance population are used as intervention strategies to control the disease. In Figure 7, it is observed that combination of treatments of infectious and drug resistance population helps in decreasing the infectious as well as the drug resistance populations. Therefore, these strategies, treatments of infectious and drug resistance population, too work effectively in eradicating the disease from human population.

4.7. Control with Education and Treatment of Infectious and Drug Resistance Population Strategies. Now, all the three control intervention strategies are applied to see how they show their impact in minimizing the objective function. In Figure 8, it is observed that combination of education and treatments of infectious and drug resistance population helps in decreasing the infectious as well as the drug resistance populations. Therefore, education and treatments of infectious and drug resistance population strategies too work effectively in eradicating the disease from human population.

5. Cost-Effectiveness Analysis

In this section, we have identified a strategy that is profitable compared to other strategies. To obtain this strategy, we used the method of incremental cost-effectiveness ratio (ICER), which is done by dividing the difference of costs between two strategies to the difference of the total number of their infections averted. This approach was defined as follows:

\[
\text{ICER} = \frac{\text{Difference in costs between strategies}}{\text{Difference in infections averted between strategies}}.
\]

(47)

The total number of infectious averted for each strategy is obtained by subtracting the total infectious with control from without control while the cost averted of each strategy was obtained by using the cost function represented by function \((1/2)w_1u_1^2 + (1/2)w_2u_2^2 + (1/2)w_3u_3^2\) over the time [25]. We did not consider strategies that implement one intervention only, due to the reason that a single intervention is not guaranteed to completely eradicate the disease from the community. Those strategies which incorporate more than one intervention are ordered below to be compared pairwise [26].

(i) Strategy A (education and treatment of individuals with infected human)

(ii) Strategy B (treatment of individuals with infected and drug resistance human)

(iii) Strategy C (education and treatment of individuals with drug resistance human)

(iv) Strategy D (education and treatment of individuals with infected and also drug resistance human)

We used parameter values in Table 1 to estimate the total cost and total infectious averted in Table 2.

After obtaining the total amount of people averted and total cost of each strategy as given in Figure 9 to compare two intervention strategies, the incremental cost-effectiveness ratio (ICER) for each competing strategy is estimated as
Figure 8: Impact of education and treatment of infectious and drug resistance on infectious and drug resistance populations.

Table 2: Total amount of infection averted and total cost for all strategies.

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Total infectious averted</th>
<th>Total cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>1,303.69</td>
<td>3464.65</td>
</tr>
<tr>
<td>C</td>
<td>4570.05</td>
<td>3712.248</td>
</tr>
<tr>
<td>D</td>
<td>4933.49</td>
<td>7117.89</td>
</tr>
<tr>
<td>A</td>
<td>4933.89</td>
<td>7176.775</td>
</tr>
</tbody>
</table>

Figure 9: Total infectious averted and the objective functional plot indicating the effect of each control strategy.

Table 3: Total amount of the infection averted and total cost with their ICER.

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Total infections averted</th>
<th>Total cost ($)</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>1,303.69</td>
<td>3464.65</td>
<td>2.66</td>
</tr>
<tr>
<td>C</td>
<td>4570.05</td>
<td>3712.248</td>
<td>0.0758</td>
</tr>
<tr>
<td>D</td>
<td>4933.49</td>
<td>7117.89</td>
<td>9.37</td>
</tr>
<tr>
<td>A</td>
<td>4933.89</td>
<td>7176.775</td>
<td>147.21</td>
</tr>
</tbody>
</table>
The amount of people averted in strategies C, B, D, and A in an increasing rank is given in Table 3.

We can observe that, from the strategies B and C in Figure 10, the ICER (C) is less than ICER (B). This implies that strategy B is dominated by strategy C. It means that strategy B is more expensive than strategy C. Thus, we have deleted B from the strategies. Then recalculate the ICER for the remaining competing strategies C, A, and D as given in Table 4.

Here the competition between interventions C and D was shown in Table 4. It is observed that the ICER (C) is less than ICER (D). This shows that strategy D is dominated by strategy C. Hence, strategy C is more efficient and less cheap than strategy D. Thus, we omitted strategy D from the list of competing and recalculated the ICER as given in Table 5.

### 6. Discussions of the Results

In this paper, we have developed deterministic epidemic model of cholera diseases with vaccination. We divided the total population of the model into five compartments, namely, susceptible, vaccinated, infective, drug resistance, and recovered, and investigated the dynamical behavior of this model. Properties of the model equations are listed: feasible region, positivity, and boundedness of model equations. Basic reproduction number is constructed, equilibrium points are identified, and their stability analysis is conducted. For the basic cholera model, control function is formulated by incorporating three control variables, namely, education and treatments of infectious and drug resistance population. Also, optimality of the control function is evaluated. The Hamiltonian, adjoint variables, and characteristic equations of control variables are formulated. Optimum control strategies of the system are derived by solving the optimal control problem. Also we numerically simulated the model equations by considering single control strategy and then by extending the number to 2 and then to 3. The impacts of the proposed strategies are investigated numerically and their results are displayed graphically.

### 7. Conclusions

A deterministic mathematical model with optimal control was intended for describing the cholera disease that is derived and analyzed to investigate the best strategies for controlling this disease by considering the minimum possible cost. The results displayed in the graphs suggest that the disease can be reduced by applying control strategies. Then also the analysis of cost-effectiveness is investigated with all the different combinations of the controls. Hence, based on the simulation result of optimality system and analysis of cost-effectiveness, we suggested that the combination of education and treatment of individuals with drug resistance human is the best effective and less costly strategy to minimize the spread of the disease.
from the community. The authors declare that this manuscript is far from being complete because of the fact that the model does not fit to the cholera real data. It is a theoretical discussion with different assumptions on the parameters and initial state variables. Therefore, we recommend any interested researchers to consider the parameter estimation of cholera disease model for more novelty.

Data Availability

The data used to support the findings of this manuscript are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References