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Modelling transmission dynamics of Ebola Virus Disease with quarantine and isolation: optimal control approach

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Abstract

Ebola virus is a virus that causes a deadly disease called Ebola virus disease (EVD). It has an average case fatality rate of 70%. EVD is a public health disease of global concern. It is endemic in Sub-Saharan Africa where it has caused several epidemics, especially the 2018 epidemic in the Democratic Republic of Congo (DRC). In this paper, a nonlinear deterministic model of EVD with quarantine and isolation as control measures is discussed. The effective reproduction number that governs the spread of the disease is calculated using next generation method. The conditions for the existence and stabilities of equilibrium states of the model are established. The sensitivity analysis of the parameters of effective reproduction number is performed using forward index method. Next, the optimal control model is presented by incorporating control efforts for quarantine and isolation. The Pontryagin's maximum principle is used to obtain the optimality system that is solved using fourth order Runge – Kutta scheme. The result indicates that quarantine and isolation measures can help eliminate the spread of EVD in the population. However, in a resource constrained setting where there is limited resources to implement both quarantine and isolation controls, it is advisable to quarantine only the exposed persons. This will be more significant in eliminating EVD in a reduced time and in return minimize the cost of control efforts, morbidity and mortality of EVD in the population.

Keywords: Ebola virus disease; quarantine; isolation; effective reproduction number; sensitivity analysis; optimal control.

1 Introduction

Ebola virus disease (EVD) is a deadly disease causes by Ebola virus. It affects human and nonhuman primates. The virus belongs to the family of filoviride and has five distinct species. These species were named according to where they were first discovered, viz; Sudan Ebola virus (SUDV),

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Tai Forest Ebola virus (TAFV), Bundibugyo Ebola virus (BDBV), Zaire Ebola virus (EBOV) and Reston Ebola virus (RESTV). Four of the species mentioned occurred in human population while RESTV caused disease in non-human population [1]. EVD epidemics have case fatality rate between 50% - 90% [2]. The natural reservoir of Ebola virus is still unknown. Although, fruit bats of the pteropodidae family are speculated to be the host of the virus [3].

More than 25 epidemics of Ebola have been recorded since the discovery of the virus in 1976. The most severe of all of them was the 2014 epidemic in West Africa that recorded 28,661 infected cases with 11,324 deaths [4]. In 2017, there was an outbreak of Ebola in Democratic Republic of the Congo (DRC) with 8 infected cases and 4 deaths [5]. Ebola epidemic was reported in DRC between April to July, 2018 with 58 infected cases and 33 deaths [6]. Thereafter, another 2018 outbreak was declared again in DRC on 1st August, 2018 Ebola epidemic. This outbreak is still going on and has recorded about 589 infected cases with 283 deaths as at 7th December, 2018 [7]. This is the 10th Ebola outbreak in DRC since the discovery of the virus in DRC (formerly Zaire) in 1976.

The incubation period of EVD is between 2 – 21 days but patients can develop symptoms after 8 – 12 days with flu-like symptoms [8]. Ebola virus is spread to human population via direct contact with blood and body fluids of infected animals. Human to human transmission occurs through direct with the blood, organs, secretion and the bodily fluids of a symptomatic person. It can also spread via surface and materials contaminated with these fluids. Aerosol transmission is not considered in human-to-human transmission of EVD since infective virions of EVD is in the oral fluid of symptomatic person [9]. People remain infectious as long as their bodily fluids contain the virus. Ebola virus is also transmitted through the semen of men who recovered for as long as three months after recovery [10].

There is no licensed drug or vaccine for Ebola virus except supportive therapy [11]. Although, there is a trial vaccine, rVSV-ZEBOV, that is given under compassionate use as a ring vaccination [12]. The control and prevention of EVD has to do with non-pharmaceutical interventions such as early identification and systematic isolation of cases, proper use of personal protection equipment, safe burial, quarantine, practice barrier nursing and so on [13,14].

Quarantine is the restriction of movement or separation of susceptible people who are exposed to a communicable diseases for a period of days that is equivalent to the incubation period of the disease [15]. On the other hand, isolation is the separation of ill persons who have a communicable disease from the healthy. It helps to stop the spread of certain diseases by restricting the movement of infected persons and treat them. The quarantine and isolation are public health practices used in reducing the prevalence or stop the spread of infectious diseases such as SARS [16]. This is crucial when there is limited resource or no licensed antiviral drug.

Several studies have been carried out to study the effect of EVD and how to halt its further spread in human population using mathematical models. Some of these studies considered different control measures. Legrand *et al.* [17] studied efficacy of interventions such as isolation and barrier nursing within the hospital using partial rank correlation coefficients and multivariate sensitivity analysis. Rachah and Torres [18] examined the effect of vaccination on the dynamics of EVD. Using the approach of sensitivity analysis, Webb *et al.* [19] identified that early identification and isolation of contact traced infection individuals will help to control the epidemics. Sule and Lawal [20] considered the effect of high risk susceptible population on EVD using optimal control approach. Tsanou *et al.* [21] studied the outcome of consumption of contaminated bush meat, funeral practices

and environmental contamination on the recurrence and persistence of EVD in Africa using stability analysis approach. Ngwa and Teboh-Ewungkem [22] studied the effect of different quarantine states for EVD and considered entering quarantine at later stages for those that escaped quarantine at the onset of the disease.

Optimal control approach is a modern extension of the calculus of variation. It helps in making policy decisions and developing optimal strategies in controlling various kinds of infectious diseases. Optimal control approach have been used by several researchers to model diseases like water-borne diseases, severe acute respiratory syndrome (SARS), Ebola virus disease and malaria. Takaidza *et al.* [23] considered the effect of quarantine, vaccination, education and safe handling of corpse of infected person on EVD while Area *et al.* [24] studied the vaccination impact on EVD. Both used the optimal control approach. As the case maybe, there is no licenced vaccine for EVD. It is important to consider the non-pharmaceutical interventions such as quarantine and isolation.

This paper investigates the impact of quarantine and isolation on the transmission dynamics of EVD using optimal control approach. It is the extension of the work by Madubueze *et al.* [25] by incorporating the exposed and recovered individuals in the formulation of the model. Exposed individuals are relevant in implementation of quarantine intervention. The existence and stabilities of the steady states are analyzed in terms of model parameters and this provides necessary conditions for the existence of steady states. The impact of the model parameters on effective reproduction number is discussed using sensitivity analysis. This is to show the most impactful parameter in eliminating EVD in the population. Furthermore, the optimal control model and the cost function are formulated and analyzed theoretically using Pontryagin's maximum principle. This will figure out the conditions that will help to determine the optimal strategies for eradicating EVD.

The paper is organized as follows. Section 2 is the formulation of the EVD model with quarantine and isolation as control measures. Section 3 is the stability, parameter estimation and sensitivity analysis of the EVD model. The optimal control approach of EVD is discussed in section 4. In Section 5, the simulation results are shown to illustrate the effects of quarantine and isolation on the spread of EVD using the data of 2018 Kivu Ebola outbreak in DRC. Thereafter, the conclusions are in Section 7.

2 Model formulation

The EVD model sub-divides the total population, $\mathrm{N}(t)$, at time, t, into sub-populations namely Susceptible, $\mathrm{S}(t)$, Exposed individuals without symptoms, $\mathrm{E}(t)$, Quarantined individuals, $\mathrm{Q}(t)$, Infected individuals with symptoms, $\mathrm{I}(t)$, individuals undergoing treatment, $\mathrm{T}(t)$ and Recovered individuals, $\mathrm{R}(t)$.

Susceptible individuals are recruited at a rate Λ. They acquire EVD through contact with infected individuals at a rate, $\frac{\beta \mathrm{I}}{\mathrm{N}}$, where β is the transmission rate. Exposed individuals may be those taking care of the infected individuals such as family or friends of the infected persons and/or the health personnel treating infected persons. The exposed individuals are traced at a rate, c_1, and progress to quarantined class for a period of twenty-one days. Within this period, any exposed individual that develop symptoms undergo treatment at a rate, ϕ. The exposed individuals without symptoms after

twenty-one days move to susceptible class at a rate, σ. Some exposed individuals that are not traced develop symptoms and progress to infected class at a rate, γ.
Inter-personal contact tracing is carried out on all persons undergoing treatment in order to pull out more infected individuals in the community. Infected individuals undergo treatment in two ways through active tracing at a rate, c_2, and isolated for treatment and through self-presentation at the hospital at a rate, α. Individuals in infected class and those undergoing treatment may die due to EVD at rates, d_1 and d_2, respectively. Natural death rate is assumed for all individuals. Those undergoing treatment recover at a rate, e. It is assumed that individuals who die of the EVD are immediately buried to prevent transmission after death.

The model is given by the following system of ordinary differential equations;

$$\frac{dS}{dt} = \Lambda - \frac{\beta SI}{N} - \mu s + \sigma Q, \quad (1)$$

$$\frac{dE}{dt} = \frac{\beta SI}{N} - \mu E - c_1 E - \gamma E, \quad (2)$$

$$\frac{dQ}{dt} = c_1 E - \varphi Q - \sigma Q - \mu Q, \quad , \quad (3)$$

$$\frac{dI}{dt} = \gamma E - \mu I - \alpha I - c_2 I - d_1 I, \quad , \quad (4)$$

$$\frac{dT}{dt} = \varphi Q + \alpha I + c_2 I - \mu T - \epsilon T - d_2 T, \quad , \quad (5)$$

$$\frac{dR}{dt} = eT - \mu R, \quad , \quad (6)$$

where $S(0) = S_0, E(0) = E_0, Q(0) = Q_0, I(0) = I_0, T(0) = T_0$ and $R(0) = R_0$ are initial conditions, assumed to be positive.

2.1 Analysis of the model

The total human population can be determined by
$N(t) = S(t) + E(t) + Q(t) + I(t) + T(t) + R(t)$.

By adding the equations (1) - (6) together, we obtain

$$\frac{dN}{dt} = \Lambda - \mu N - d_1 I - d_2 T. \quad (7)$$

N is asymptotically equal to $\frac{\Lambda}{\mu}$, i.e. $N \approx \frac{\Lambda}{\mu}$ when d_1, d_2 are negligible. Therefore, $N(t) \leq \frac{\Lambda}{\mu}$.

3.1 Well-Posedness of the Model

In this section, we prove that Ebola transmission model is well-posed. This is done by the proving that the positivity, boundedness, existence and uniqueness of the solutions of model with non-negative initial data remain non-negative for all time. We state the positively invariant region.

Lemma 1. The set $\Omega = \left\{(S, E, Q, I, T, R) \in \mathbb{R}_+^6 : N \leq \frac{\Lambda}{\mu}\right\}$ is positively invariant with respect to the Ebola model (1) - (6).

Lemma 2 (Positivity): Let the set of initial solution be $\{(S(0), E(0), Q(0), I(0), T(0), R(0)) \in \Phi\}$. Then, the solution set $\{S(t), E(t), Q(t), I(t), T(t), R(t)\}$ of the Ebola transmission model is non-negative for $t > 0$.

Proof:
Assume that the set of initial solutions, $\{(S(0), E(0), Q(0), I(0), T(0), R(0)) \geq 0\}$, then equation (1) can be written as

$$\frac{dS}{dt} \geq \Lambda - \left(\frac{\beta I}{N} + \mu\right) S = \Lambda - \beta(t) S \quad (8)$$

where $\beta(t) = \frac{\beta I}{N}$.

Equation (8) is a linear first order ordinary differential equation in S with the solution

$S(t) = S(0) exp\left(\int_0^t -\beta(S) ds\right) \times \int_0^t \Lambda exp\left(\int_0^u \beta(\omega) d\omega\right) \geq 0.$

Hence, $S(t) \geq 0 \quad \forall \quad t \geq 0.$

In similar way, the remaining state variables are obtained such as:

$E(t) \geq E(0)\, Exp(-(\mu + c_1 + \gamma)) \geq 0,$
$Q(t) \geq Q(0)\, Exp(-(\varphi + \delta + \mu)) \geq 0,$
$I(t) \geq I(0) Exp\left(-(\mu + \alpha + c_2 + d_1)\right) \geq 0,$
$T(t) \geq T(0)\, Exp(-(\mu + e + d_2)) \geq 0,$
$R(t) \geq R(0)\, Exp(-\mu) \geq 0.$

This completes the proof of the Lemma 1.

Lemma 3: (Boundedness) Assume that the initial condition for Ebola model (1) – (6) satisfies $N(0) \leq \frac{\Lambda}{\mu}$. Then, whenever the solution exists on an interval J, it satisfies the following boundedness

$N(t) \leq \frac{\Lambda}{\mu}$.

Proof:
Since $I(t) \geq 0$, we have from (7) that $\frac{dN}{dt} < \Lambda - \mu N$.
Applying the Gronwall's inequality gives
$N(t) \leq \frac{\Lambda}{\mu} + \left(N(0) - \frac{\Lambda}{\mu}\right) e^{-\mu t}$ whenever $(0) \leq \frac{\Lambda}{\mu}$. We have $N(t) \leq \frac{\Lambda}{\mu}$. Consequently, $I(t) \leq \frac{\Lambda}{\mu}$
.
.
Lemma 4: (Existence and Uniqueness) Let $t^* > 0$, if the initial condition satisfy $\{(S(0), E(0), Q(0), I(0), T(0), R(0)) > 0\}$. Then,$\forall\, t \in \mathbb{R}$, the solution set $\{S(t), E(t), Q(t), I(t), T(t), R(t)\}$ exists in R_+^6 and is unique.

Proof:

The model (1) – (6) is rewrite as

$$X = \begin{bmatrix} S(t) \\ E(t) \\ Q(t) \\ I(t) \\ T(t) \\ R(t) \end{bmatrix} \text{ and } F(x) = \begin{bmatrix} \Lambda - \frac{\beta SI}{N} - \mu s + \sigma Q \\ \frac{\beta sI}{N} - \mu E - c_1 E - \gamma E \\ c_1 E - \varphi Q - \sigma Q - \mu Q \\ \gamma E - (\mu + d_1 + c_2 + \alpha) I \\ (c_2 + \alpha) I + \varphi Q - (\mu + e + d_2) T \\ eT - \mu R \end{bmatrix}.$$

Here, F is continuous and locally satisfies Lipschitz condition in R_+^6 . Using the Picard-Lindelof Theorem and the Lemmas 1 and 2 that proved the positivity and boundedness of solutions, there exists $t^* > 0$ such that the solution set of the Ebola model (1) - (6) exists locally at least on an interval $[0, t^*]$ and is unique. Therefore, the biological validity of the model (1) - (6) is stated in Lemma 4.

Lemma 5: The Ebola model (1) - (6) is well posed and valid in the set
$\left\{\Omega = \{S(t), E(t), Q(t), I(t), T(t), R(t)\} \in R_+^6;\ N \leq \frac{\Lambda}{\mu}\right\}$.

3.2 Steady States and Stability analysis

The disease - free equilibrium state of the EVD model is derived by equating the derivatives of Equations (1) – (6) to zero and solve for $I(t) = 0$. This is given as
$E_0 = \left[\frac{\Lambda}{\mu}, 0,0,0,0, 0\right]$.

The effective reproduction number, $R_{e,}$ is calculated using the next generation approach [26]. It is given by

$$R_e = \frac{\beta\gamma}{(\mu+c_1+\lambda)(\mu+\alpha+d_1+c_2)} = \frac{\beta\gamma}{fh} \tag{9}$$

where

$$f = \mu + c_1 + \lambda,\ g = \varphi + \delta + \mu\ , h = \mu + \alpha + d_1 + c_2 \text{ and } m = \mu + e + d_2. \tag{10}$$

Using the theorem in Driessche and Watmough [26], we have that the disease-free equilibrium of the EVD model (1) – (6) is locally asymptotically stable if $\mathrm{R_e} < 1$ and unstable if $\mathrm{R_e} > 1$.

3.3 Existence of Endemic Equilibrium State

Let $E_1 = [S^*, E^*, Q^*, I^*, T^*]$ be any arbitrary endemic equilibrium state of the model (1) - (6). Let the force of infection be represented by

$\lambda \leftleftharpoons \frac{\beta I}{N}$.

Equating the derivatives of the EVD model (1) - (6) to zero and solve resulting equations simultaneously in terms of λ, we obtain

$S^* = \frac{fg\Lambda}{\lambda(fg-\sigma c_1)+fg\mu}$, $E^* = \frac{g\Lambda\lambda}{\lambda(fg-\sigma c_1)+fg\mu}$, $Q^* = \frac{\lambda c_1 \Lambda}{\lambda(fg-\sigma c_1)+fg\mu}$, $I^* = \frac{g\Lambda\lambda\gamma}{h[\lambda(fg-\sigma C_1)+fg\mu]}$,

$T^* = \frac{\lambda\Lambda(\alpha g\gamma+g\gamma c_2+h\varphi c_1)}{hm(\lambda(fg-\sigma c_1)+fg\mu)}$, $R^* = \frac{eT^*}{\mu}$,

where $f = \mu + c_1 + \gamma$; g = φ + σ + μ; $h = c_2 + \alpha + \mu + d_1$; $m = \mu + d_2 + e$; $fg - \sigma c_1 = f(\varphi + \mu) + (\mu + \gamma)\sigma$.

Substituting $S^*, E^*, Q^*, I^* T^*, R^*$, in $= \frac{\beta I^*}{N^*}$, where $N^* = S^* + E^* + Q^* + I^* + T^* + R^*$
and simplify to give $A\lambda + B = 0$,
where $A = K\mu + g\gamma m\mu + Ke + ghm\mu + hmc_1\mu$; $B = mg\mu(fh - \beta\gamma)$, $K = \alpha g\gamma + g\gamma c_2 + h\varphi c_1$. Using (9), we have $B = mgfh\mu(1 - R_e)$.

It is evidence that A is positive and B is positive (negative) whenever R_e is less than (greater than) one. If $B > 0$, no endemic equilibrium state exists, then the forward bifurcation exists. This implies that an endemic equilibrium state exists only if $B < 0$. This is given by

$\lambda = \frac{mgfh\mu(R_e - 1)}{A}$.

Substituting $\lambda = \frac{mgfh\mu(R_e - 1)}{A}$ into S^*, E^*, Q^*, I^* and T^*, this gives

$S^* = \frac{\Lambda A}{[hm\mu(f\gamma + \mu f + c_1\varphi + c_1\mu)(R_e - 1) + A\mu]}$; $E^* = \frac{fhm\Lambda\mu(R_e - 1)}{P}$; $Q^* = \frac{c_1 hm\Lambda\mu(R_e - 1)}{P}$; $I^* = \frac{g\gamma m\Lambda\mu(R_e - 1)}{P}$
and $T^* = \frac{(\alpha g\gamma + g\gamma c_2 + h\varphi c_1)\Lambda\mu(R_e - 1)}{P}$
where $P = hm\mu(\gamma g + \mu g + c_1\varphi + c_1\mu)(R_e - 1) + A\mu$.

This leads to the following theorem.
Theorem 1. The model equations (1) - (6) has a unique endemic equilibrium (EE) state whenever $R_e > 1$.

3.4 Global Stability Analysis of Equilibrium States

In this section, the global stability analysis of two equilibrium states, DFE and EE states are considered since the bifurcation is forward.

Theorem 2. The disease-free equilibrium (DFE) state of the model equations (1) – (6) is global asymptotically stable on Ω whenever $R_e < 1$.

Proof:

The Lyapunov function $L(t)$ is formulated as
$L(t) = \frac{\gamma}{fh}E + \frac{1}{h}I$.

The derivative of $L(t)$ along the solutions of (1) – (6) is given by
$L'(t) = \frac{\gamma}{fh}\left[\frac{\beta SI}{N} - fE\right] + \frac{1}{h}(\gamma E - hI)$.

Evaluating at the DFE gives
$L'(t) = \left[\frac{\beta\gamma}{fh} - 1\right]I - \frac{\beta\gamma I}{fh}\left[1 - \frac{S}{N}\right]$

Since S$\leq N$, then it implies that $S/N \leq 1$.

Hence, using the definition of $R_e$in (9), we have
$L'(t) \leq \left(\frac{\beta\gamma}{fh} - 1\right) I = (R_e - 1)I$.

Since all the parameters are non-negative, it means that $L'(t) \leq 0$ if $R_e < 1$. By LaSalle's invariance principle which state that every solution of the model (1) – (6) tends to DFE, E_0, as $t \to \infty$ whenever $R_e < 1$.

Next, the global stability of endemic equilibrium state with the special case that disease induce death rates $d_1, d_2 = 0$ is studied, so that $N(t) \to \Lambda/\mu$ asymptotically. Then, $\frac{\beta SI}{N} = \bar{\beta} SI$ where $\bar{\beta} = \frac{\beta\mu}{\Lambda}$.

Theorem 3. The unique positive endemic equilibrium state of the EVD model is globally asymptotically stable in the absence of disease-induced death rates, $d_1, d_2 = 0$, whenever $R_e > 1$, $Q \leq Q^*$ and $I \leq I^*$.

Proof:

We construct non-linear Lyapunov function

$$L = \left(S - S^* - S^* \ln\frac{S}{S^*}\right) + \left(E - E^* - E^* \ln\frac{E}{E^*}\right) + \left(Q - Q^* - \mathrm{Q}^* \ln\frac{Q}{Q^*}\right) + \frac{\bar{\beta} S^* I^*}{\gamma E^*}\left(I - I^* - I^* \ln\frac{I}{I^*}\right) + \left(T - T^* - T^* \ln\frac{T}{T^*}\right).$$

The associated derivative of $L(t)$ along the solutions of the EVD model is given as

$$L'(t) = \left(1 - \frac{S^*}{S}\right)\left(\Lambda - \bar{\beta} SI - \mu S + \sigma Q\right) + \left(1 - \frac{E^*}{E}\right)\left(\bar{\beta} SI - fE\right) + \left(1 - \frac{Q^*}{Q}\right)[c_1 E - gQ] + \frac{\bar{\beta} S^* I^*}{\gamma E^*}\left(1 - \frac{I^*}{I}\right)(\gamma E - hI) + \left(1 - \frac{T^*}{T}\right)(\alpha I + c_2 I + \varphi Q - mT) \quad (11)$$

At steady state, we have
$\Lambda = \bar{\beta} S^* I^* + \mu S^* - \sigma Q^*$; $f = \frac{\bar{\beta} S^* I^*}{E^*}$; $g = \frac{c_1 E^*}{Q^*}$; $h = \frac{\gamma E^*}{I^*}$; $m = \frac{(\alpha + c_2) I^* + \varphi Q^*}{T^*}$

Expanding and evaluating (11) at steady state gives

$$L'(t) = \bar{\beta} S^* I^* + \mu S^* - \sigma Q^* - \mu S + \sigma Q - \frac{\bar{\beta} S^{*2} I^*}{S} - \frac{\mu S^{*2}}{S} + \frac{\sigma Q^* S^*}{S} + \bar{\beta} S^* I + \mu S^* - \frac{\sigma Q S^*}{S} - \frac{\bar{\beta} S^* I^* E}{E^*} + \bar{\beta} S^* I^* - \frac{\bar{\beta} S I E^*}{E} - \bar{\beta} S^* I - \frac{\bar{\beta} S^* I^{*2} E}{E^* I} + \bar{\beta} S^* I^* + \frac{\bar{\beta} S^* I^* E}{E^*} + c_1 E - \frac{c_1 E^* Q}{Q^*} - c_1 E \frac{Q^*}{Q} + c_1 E^* + (\alpha I + c_2 I + \varphi Q - \frac{(\alpha + c_2) I^*}{T^*} T - \frac{\varphi Q^*}{T^*} T - \frac{(\alpha + c_2) I}{T} T^* - \frac{\varphi Q}{T} T^* + (\alpha + c_2) I^* + \varphi Q^* \quad (12)$$

Upon simplification, equation (12) is given as

$$L'(t) = \bar{\beta}S^*I^*\left(3 - \frac{S^*}{S} - \frac{EI^*}{E^*I} - \frac{SIE^*}{S^*I^*E}\right) + \sigma Q^*\left(\frac{S^*}{S} - \frac{S^*Q}{SQ^*} + \frac{Q}{Q^*} - 1\right) + \mu S^*\left(2 - \frac{S^*}{S} - \frac{S}{S^*}\right) +$$
$$c_1E^*\left(1 + \frac{E}{E^*} - \frac{EQ^*}{E^*Q} - \frac{Q}{Q^*}\right) + (\alpha + c_2)I^*\left(1 + \frac{I}{I^*} - \frac{IT^*}{I^*T} - \frac{T}{T^*}\right) + \varphi Q^*\left(1 + \frac{Q}{Q^*} - \frac{QT^*}{Q^*T} - \frac{T}{T^*}\right)$$

Using the assumption that $Q \leq Q^*$ and $I \leq I^*$, it follows that

$$\left(\frac{S^*}{S} - \frac{S^*}{S}\frac{Q}{Q^*} + \frac{Q}{Q^*} - 1\right) \leq 0, \quad \left(1 + \frac{I}{I^*} - \frac{IT^*}{I^*T} - \frac{T}{T^*}\right) \leq \left(2 - \frac{T^*}{T} - \frac{T}{T^*}\right), \quad \left(1 + \frac{Q}{Q^*} - \frac{QT^*}{Q^*T} - \frac{T}{T^*}\right) \leq$$
$\left(2 - \frac{T^*}{T} - \frac{T}{T^*}\right)$ and $\left(1 + \frac{E}{E^*} - \frac{EQ^*}{E^*Q} - \frac{Q}{Q^*}\right) \leq \frac{E}{E^*}\left(1 - \frac{Q^*}{Q}\right)$.

By the arithmetic-geometric mean theorem, the following inequalities hold:

$$3 - \frac{S^*}{S} - \frac{EI^*}{E^*I} - \frac{SIE^*}{S^*I^*E} \leq 0\,; \quad 2 - \frac{S^*}{S} - \frac{S}{S^*} \leq 0 \quad ; \quad 2 - \frac{T^*}{T} - \frac{T}{T^*} \leq 0 \; ; \; \left(1 - \frac{^*}{}\right) \leq 0 \; .$$

Therefore, $'() \leq 0$ for > 1 since all the parameters of the model are non-negative. It means that $'()$ is a Lyapunov functions. In addition, $'() = 0$ if and only if $= ^*, = ^*, = ^*, = ^*, = ^*$ and $= ^*$.
By the LaSalle's Invariance principle, we conclude that the endemic equilibrium state is globally asymptotically stable whenever > 1 and $_1, _2 = 0$, $\leq ^*$ and $\leq ^*$.

3.5 Parameter estimation

The second 2018 DRC Ebola epidemic started in North Kivu, the Eastern part of DRC. This was reported officially by WHO on 1st August, 2018 with 4 confirmed cases, 22 probable cases and 20 deaths [27]. The population of North Kivu is estimated at 5767945 in the year 2018 [28]. From the data of North Kivu outbreak, the initial conditions are estimated as follows: the initial susceptible individuals, $(0) = 5767945 - 26 = 5767919$, the initial infected individuals, $(0) = 20$, the individuals undergoing treatment, $(0) = 26 - 20 = 6$ and the initial recovery individuals, $(0) = 0$. The initial quarantined individuals, (0), is computed as the difference between 1st August, 2018 and 24th August, 2018 from the 2018 Kivu Ebola data, since the incubation period of EVD falls within the period. This is given as $(0) = 117 - 26 = 91$. For EVD, the average incubation period for exposed individuals ranges between 8 to 10 days [29]. Therefore, the incubation period for exposed individuals is taken as 8 days. So the initial exposed individuals is as $(0) = 76$ (that is the difference between the reported infected cases at first day and tenth day).

The crude birth rate of DRC is assume to be the birth rate, Λ, in this study and is given as 32. [30]. The natural death rate, , is the reciprocal of life expectancy of DRC and is estimated as $= \frac{1}{58.3} = 0.0172^{-1}$. The death due to the disease for the infected individuals and those undergoing treatment are estimated from the case fatality rate of the 2018 Ebola DRC outbreak as $_1 = 0.0673$ and $_2 = 0.0556$, respectively [28]. The transfer rate from quarantine to susceptible class after incubation period of 21 days is computed as $= \frac{1}{21} = 0.0476^{-1}$. The other parameter values are taken from Ivorra and Ramos [31]. The Table 1 presents the parameter values of the EVD model.

The number of infectious cases and dead cases of the 2018 Kivu Ebola outbreak are presented in Figure 1 and 2, respectively.

Parameter	Value $(day)^{-1}$	Source	Parameter	Value $(day)^{-1}$	Source
	0.36	Ivorra and Ramos (2018)	$_2$	Variable	Assumed
	[0.2, 0.5]	„		0.0476	Estimated
	[0.14,0.2]	„	$_1$	0.0673	„
	0.0877	„	$_2$	0.0556	„
	variable	Assumed		0.0172	„
	variable	Assumed	Λ	32	„

Table 1: Parameter values of the EVD Model

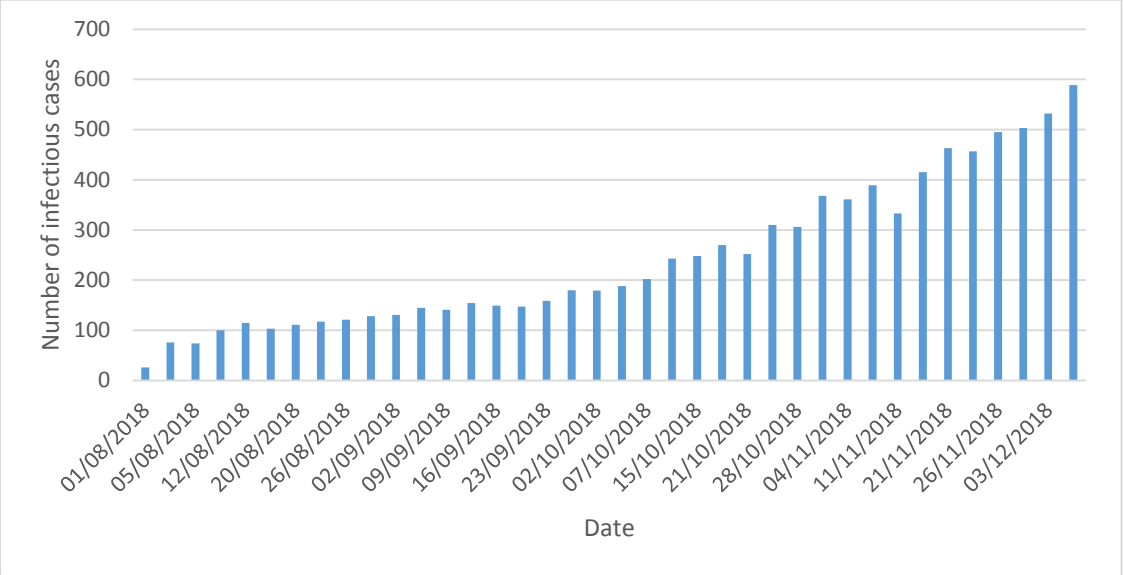


Figure 1. Number of reported infectious cases of 2018 Kivu Ebola outbreak

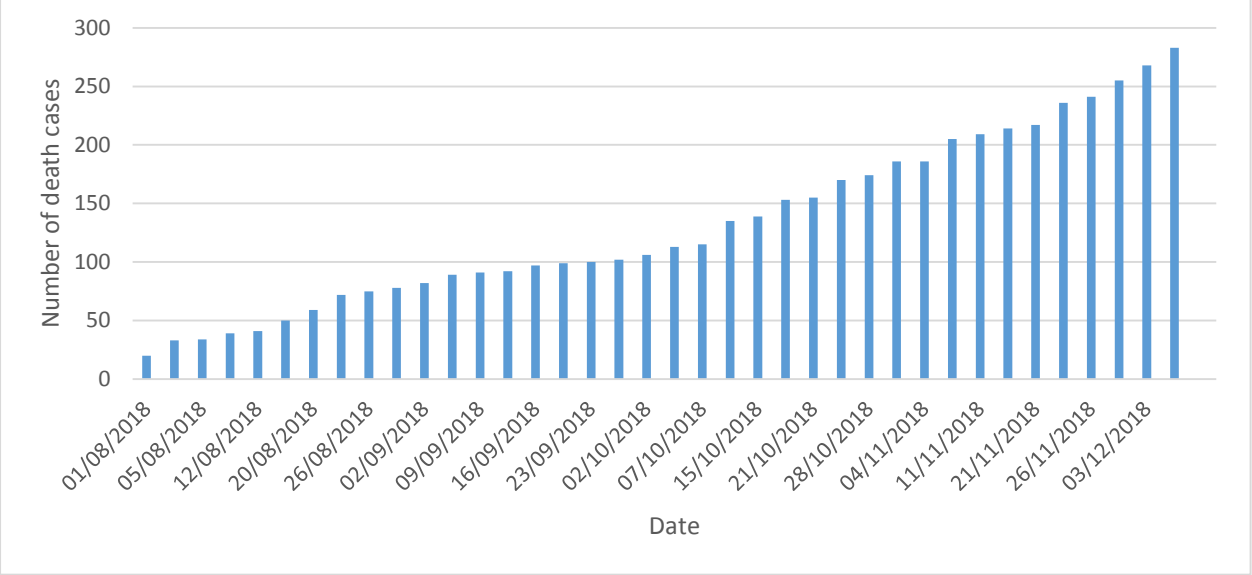


Figure 2. Number of reported death cases of 2018 Kivu Ebola outbreak

3.6 Sensitivity Analysis of the Model Parameters

The sensitivity analysis is performed to show the important of each model parameter in controlling infectious disease in the population. This helps to determine the parameters that have the highest impact in reducing effective reproduction number, . It is also used to investigate the model robustness to parameter values since data collection and presumed parameter values may have errors.

The normalized forward sensitivity index method is used to investigate this.

Definition 1. The normalized forward sensitivity index of a variable, , that depends differentially on a parameter is defined as $\Upsilon = \times$.

The sensitivity index of with respect to each parameter of using the parameter values in Table 1 is given in Table 2. For example, the sensitivity index of with respect to is $\Upsilon = \times = 0.1264$.

The sensitivity indices are arranged in Table 2 from the most sensitivity index value to the least. The positive indices imply that an increase in the respective parameters $(,)$ will increase the effective reproduction number, while the negative indices indicate that decreases when the corresponding parameters $(_1, _2,)$ increase.

Parameter	Sign of Index	Sensitivity Index Value
	+	0.4542
	+	0.1264
	−	0.1108
	−	0.0645
	−	0.4621
	−	0.4621
	−	0.4621

Table 2. Sensitivity indices of of the EVD Model

4 Analysis of optimal control

In this section, the time dependent quarantine, $u_1(t)$and isolation, $u_2(t)$ control efforts are examined. This is to investigate how much time is needed in implementing quarantine and isolation measures in order to halt further spread of EVD.
The optimal control model is given by

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{\beta SI}{N} + \sigma Q - \mu S \\
\frac{dE}{dt} &= \frac{\beta SI}{N} - (\gamma + \mu + u_1(t)c_1)E \\
\frac{dQ}{dt} &= u_1(t)c_1E - gQ \\
\frac{dI}{dt} &= \gamma E - \big(\mu + \alpha + d + c_2u_2(t)\big)I \\
\frac{dT}{dt} &= \varphi Q + c_2u_2(t)I + \alpha I - mT \\
\frac{dR}{dt} &= eT - uR
\end{aligned} \tag{12}$$

where g, m are defined in (11) and $U = \{(u_1, u_2)\ is\ measurable\ and\ 0 \leq u_1, u_2 \leq 1\ for\ t\epsilon[0, t_1]\}$ is the control effort set.

The function, $u_1(t)$, represents preventive measure in using quarantine measure such as setting up quarantine centre and hiring of health centre giver, equipping the quarantine centre, etc. This helps in reducing the interactions between the infected and susceptible individuals. The function, $u_2(t)$, represents the efforts used in isolating the infectious individuals traced in the population. These efforts include prompt treatment, supportive therapy and close monitoring of infected persons.
To minimize the number of infected individuals and the cost of applying these controls, quarantine and isolation, the objective functional, J is construct and is given by

$$J = \int_0^{t_1} AI(t) + \frac{1}{2}B_1u_1^2(t) + \frac{1}{2}B_2u_2^2(t)dt \tag{13}$$

This is subject to the system of differential equations (12).

Here, t_1 is the final time of the intervention and the coefficient A, B_1, B_2 are positive weights in balancing the cost factors. The term AI is cost of infection while $\frac{1}{2}B_1u_1^2(t)$ and $\frac{1}{2}B_2u_2^2(t)$ are the costs of implementing quarantine and isolation respectively.

We seek an optimal control u_1^* and u_2^* such that

$$J(u_1^*, u_2^*) = min_{u_1, u_2 \epsilon U} J(u_1, u_2)$$

where $U = (u_1^*, u_2^*)$ is defined as before.

Fleming and Rishel [32] guarantee the existence of optimal control model. The necessary conditions that an optimal control model must satisfy come from the Pontryagin's maximum principle [33]. This principle converts (12) and (13) into a problem of minimizing pointwise a Hamiltonian, H and is given by

$$H = AI(t) + \frac{1}{2}B_1 u_1^2(t) + \frac{1}{2}B_2 u_2^2(t) + \lambda_1\left(\Lambda - \frac{\beta SI}{N} + \delta Q - \mu S\right) + \lambda_2\left(\frac{\beta SI}{N} - (\gamma + \mu + u1c1E + \lambda 3u1c1E - gQ + \lambda 4\gamma E - \mu + d + \alpha + u2c2I + \lambda 5\varphi Q + u2c2I + \alpha I - mT + \lambda 6(eT - \mu R)\right.$$

where $\lambda_i, i = 1 - 6,$ are the adjoint variables or co-state variables.

By applying Pontryagin's maximum principle and the existence result for the optimal control model from Fleming and Rishel [32], the following proposition is obtained.

Proposition 2. Given an optimal control pair $\left(u_1^*(t), u_2^*(t)\right)$ that minimize $J(u_1, u_2)$ over U. Then there exists adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6$ satisfying

$$\left.\begin{aligned}
\frac{d\lambda_1}{dt} &= \left(\frac{\beta I}{N} - \frac{\beta SI}{N^2}\right)(\lambda_1 - \lambda_2) + \mu\lambda_1 \\
\frac{d\lambda_2}{dt} &= \frac{\beta SI}{N^2}(\lambda_2 - \lambda_1) + \mu\lambda_2 + u_1 c_1(\lambda_2 - \lambda_3) + \gamma(\lambda_2 - \lambda_4) \\
\frac{d\lambda_3}{dt} &= \frac{\beta SI}{N^2}(\lambda_2 - \lambda_1) + \mu\lambda_3 + \sigma(\lambda_3 - \lambda_1) + \varphi(\lambda_3 - \lambda_5) \\
\frac{d\lambda_4}{dt} &= \left(\frac{\beta S}{N} - \frac{\beta SI}{N^2}\right)(\lambda_1 - \lambda_2) + \lambda_4(\mu + d_1) + (u_2 c_2 + \alpha)(\lambda_4 - \lambda_5) - A \\
\frac{d\lambda_5}{dt} &= \lambda_5(\mu + d_2) + \frac{\beta SI}{N^2}(\lambda_2 - \lambda_1) + e(\lambda_5 - \lambda_6) \\
\frac{d\lambda_6}{dt} &= \lambda_6\mu + \frac{\beta SI}{N^2}(\lambda_2 - \lambda_1)
\end{aligned}\right\} \quad (14)$$

with transversality conditions

$$\lambda_1(t_1) = \lambda_2(t_1) = \lambda_3(t_1) = \lambda_4(t_1) = \lambda_5(t_1) = \lambda_6(t_1) = 0 \quad (15)$$

and optimality conditions is given as

$$u_1^* = \frac{c_1 E^* (\lambda_2 - \lambda_3)}{B_2} \quad ; \quad u_2^* = \frac{c_2 I^* (\lambda_4 - \lambda_5)}{B_3} \quad (16)$$

Proof:

The system of differential equations in (14) is obtained by differentiation of Hamiltonian function, H, evaluated at the optimal control. This is written as

$-\frac{d\lambda_1}{dt} = \frac{\partial H}{\partial S}$, $-\frac{d\lambda_2}{dt} = \frac{\partial H}{\partial E}$, $-\frac{d\lambda_3}{dt} = \frac{\partial H}{\partial Q}$, $-\frac{d\lambda_4}{dt} = \frac{\partial H}{\partial I}$, $-\frac{d\lambda_5}{dt} = \frac{\partial H}{\partial T}$ and $-\frac{d\lambda_6}{dt} = \frac{\partial H}{\partial R}$.

In addition, equating to zero the derivative of Hamiltonian with respect to the control variables in the interior of the control set, U, that is

$\frac{\partial H}{\partial u_1} = 0$, $\frac{\partial H}{\partial u_2} = 0$ and $\frac{\partial H}{\partial u_3} = 0$, we solve for u_1 as u_1^* and u_2 as u_2^*.

This is given as $u_1^* = \frac{c_1 E^* (\lambda_2 - \lambda_3)}{B_1}$ and $u_2^* = \frac{c_2 I^* (\lambda_4 - \lambda_5)}{B_2}$.

Using the bounds on the controls, we derived the optimality conditions as follows
$u_1^* = max\{0, min(1, \omega_1)\}$ and $u_2^* = max\{0, min(1, \omega_2)\}$,
where $\omega_1 = \frac{c_1 E^* (\lambda_2 - \lambda_3)}{B_1}$ and $\omega_2 = \frac{c_2 I^* (\lambda_4 - \lambda_5)}{B_2}$.

Remark: Due to the pair boundedness of the state and adjoint functions and the resulting Lipschitz structure of the ODE's, the uniqueness of the optimal control for small time is obtained. The uniqueness of the optimal control follows from the uniqueness of the optimality system, which consists of (14) and (15) with characterization (16). There is restriction of the length of time interval in order to guarantee the uniqueness of the optimality system. The smallest in length is resulting from the opposite time orientation of (14) and (15); the state problem has initial values and the adjoint problem has final values. This restriction is very common in control problem (see, [34])
Next, the numerical results of the optimality system and the optimal control strategies, the choice of parameter values and the interpretations of various control strategies will be discussed.

5 Numerical results and discussions

In this section, the numerical simulation of the optimal control strategies of the transmission dynamics of EVD is presented. The fourth order Runge-Kutta scheme is used to solve the optimality system that consists of state system and adjoint system. The initial guess of the control variables in Table 1 is used to solve the optimality system for the different simulations. Different values of the state and adjiont solutions are used in the process continue repeatedly until convergence of the solutions (state, adjoint and control effort values) are achieved. The details of the scheme are in Lenhart and Workman [35].

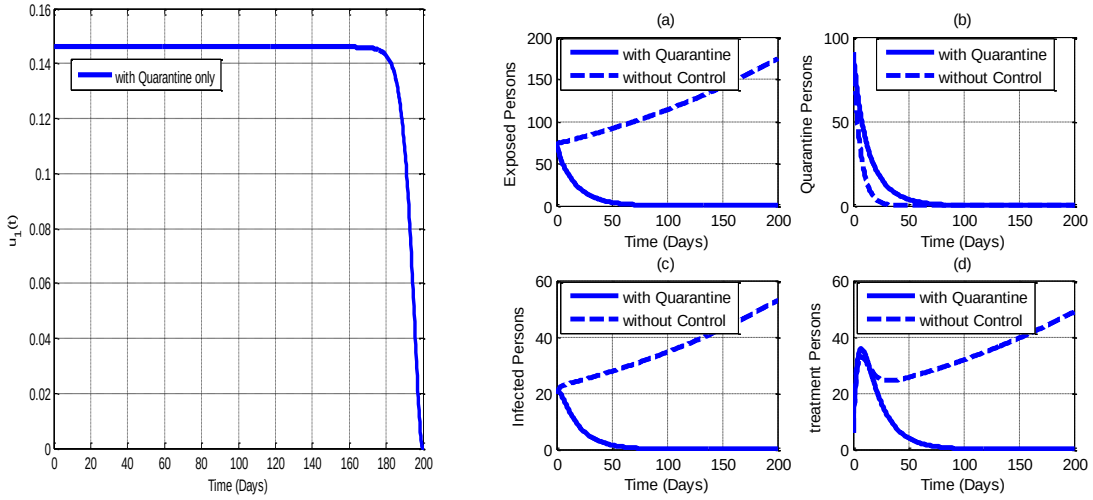
The parameter values and initial conditions used in the simulation are stated in Table 1. The entire period considered in this work is $T = 200$ days. The weight cost parameters are given as $A = 0.02, B_1 = 10$ and $B_2 = 5$. The weight cost, B_1, associated with u_1 is assumed to be greater than the weight costs, B_2 that are associated with u_2. This is because the cost of quarantine exposed individual, B_1, involves setting up quarantine centre, hiring of health care workers, equipping the quarantine centre and the logistics of monitoring the quarantine individuals while the cost of

isolating the infectious individuals, B_2, involves supportive therapy and treatment for the infected person isolated.

A deterministic model of EVD transmission with the effects of quarantine and isolation is examined.

5.1 Optimal Quarantine of Exposed Individuals

The quarantine of exposed individuals, u_1, is used to optimize the objective function, J. In Figure 3, it is observed that the disease-free equilibrium state is achieved between fifty to sixty days. It also reduces the number of exposed, infected and treatment persons while increases the number of quarantined persons. This happens when the quarantine control u_1 is maintained at the upper bounds for 180 days before dropping gradually to its lower bound zero (Figure 3(a)). This implies that EVD can be controlled if proper quarantine of exposed persons is carried out immediately.

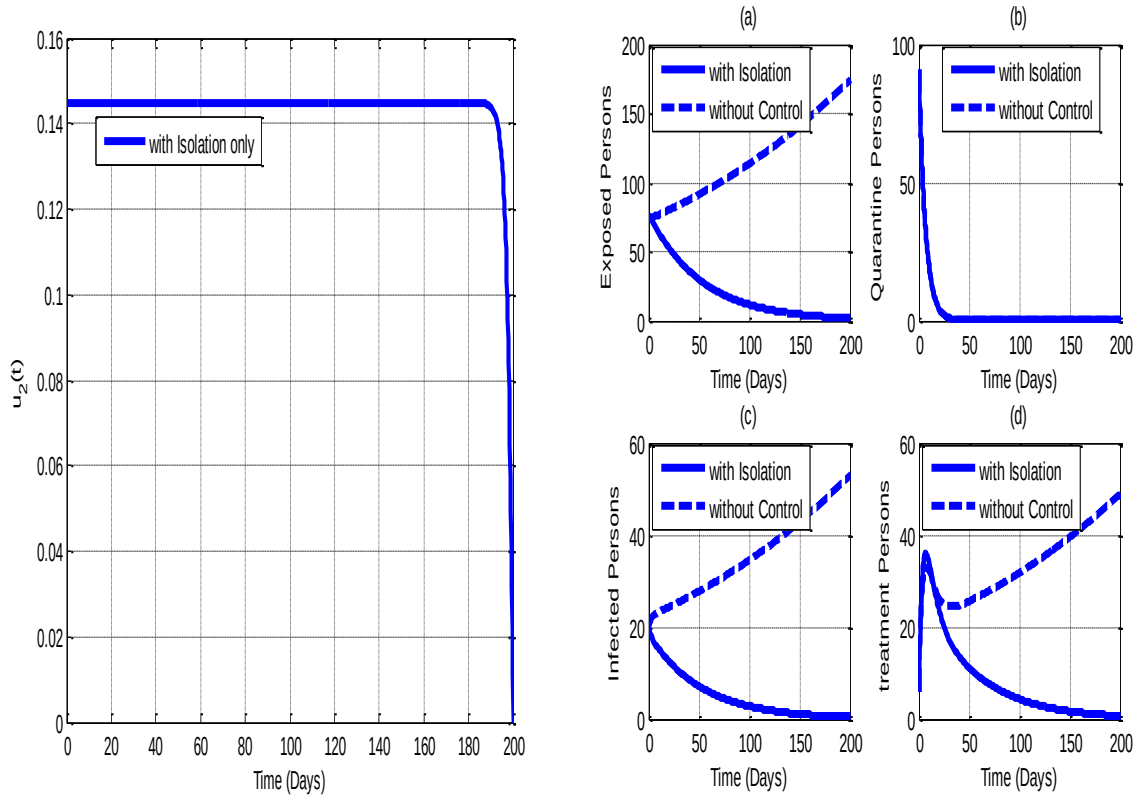


(a) u_1 control (b) u_1 profile

Figure 3. Simulation results for optimal quarantine only and without controls.

5.2 Optimal Isolation of Infected Individuals

In this case, the isolation of infected individuals, u_2, is used to optimize the objective function, J. In Figure 4, it is observed that the disease-free equilibrium state is achieved between 150 to 170 days. It reduces the number of exposed, infected and treatment persons but do not affect quarantined persons. The isolation control, u_2, is maintained at the upper bounds for 190 days and drops rapidly to its lower bound zero. This indicates that isolation of infected person can eliminate EVD in the population but it requires more days to achieve that. The more days may result to high cost of control implementation, morbidity and mortality of EVD in the population.

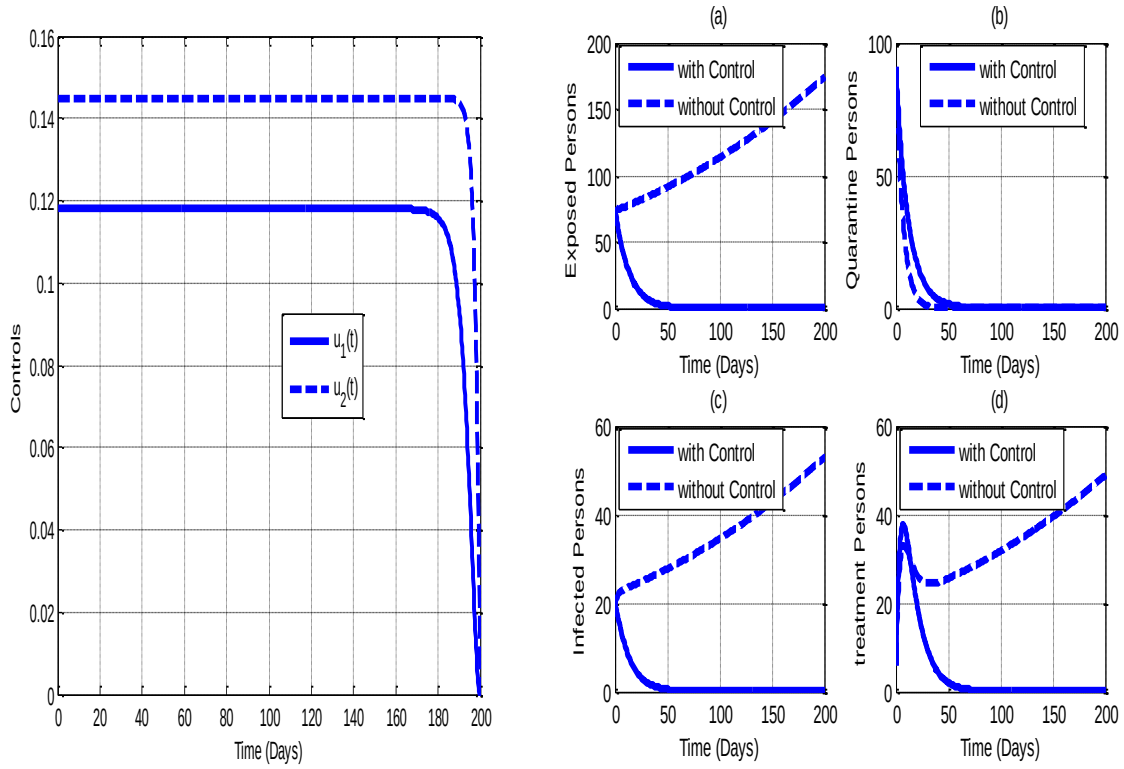


u_2 control (b) u_2 profile

Figure 4. Simulation results for optimal isolation only and without controls.

5.3 Optimal quarantine and isolation

The quarantine control, u_1, and isolation control, u_2, is used to optimize the objective function, J. It is presented in Figure 5. When both controls are implemented simultaneously, the disease-free equilibrium state is achieved within 45 to 48 days of the outbreak. The quarantine control, u_1, is maintained at the upper bounds for 170 days and drops gradually to zero while isolation control, u_2, is maintained at the upper bounds for 195 days and drops rapidly to its lower bound zero. This implies that quarantine and isolation controls can eliminate EVD in the population. However, without the control measures the EVD remains endemic in the population. The simultaneous implementation of quarantine and isolation controls take less days (165 days) to obtain disease-free equilibrium state compare to when only quarantine or only isolation is carried out . Thus, in a situation where it is difficult to carry out the two controls simultaneously either due to cost or man power, it is advisable to quarantine only the exposed persons in the population.



(a) u_1 and u_2 controls (b) u_1 and u_2 profile

Figure 5. Simulation results for optimal quarantine and isolation and without controls.

Conclusion

A deterministic model for the transmission dynamics of EVD with quarantine and isolation measures is formulated and analyzed in this paper. The effective reproduction number, R_e is computed and existence and stabilities of the equilibrium states are investigated. The sensitivity of the parameters of R_e is performed and these parameters, λ and β are the most sensitive parameters. The necessary conditions for optimal control of EVD with quarantine and isolation are derived and analyzed. The numerical results showed that quarantine and isolation controls will eradicate the EVD transmission in the population. However, in a resource constrained setting where there is limited resources to implement both quarantine and isolation controls, it is advisable to quarantine only the exposed persons. This will be more significant in eliminating EVD in a reduced time and in return minimize the cost of control efforts, morbidity and mortality of EVD in the population.

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