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Mathematical Analysis of an Ebola Model with Carriers, Relapse and Re-infection

Brenda Achieng Onyango [a*]

[a] *Department of Mathematics, Masinde Muliro University of Science and Technology, Kenya.*

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Original Research Article

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Abstract

Ebola virus disease (EVD) is a zoonotic filovirus caused by an RNA virus of the family *filoviridae* and genus *Ebolavirus*. It is transmitted by direct human to human contact via body fluids or indirect contact with contaminated surfaces. Due to its transmission mode the disease spreads so fast. The previous outbreaks have caused high mortality rates of up to 90%. Currently African countries like Democratic Republic of Congo and Uganda are experiencing a re-occurrence of EVD oubreak. The porous borders between African countries has always been an issue of concern with relevant authorities not taking meaningful measures to control cross border movement of persons. This poses a challenge to health systems especially in Kenya which is at a close proximity to Uganda. Ebola virus is known to persist in the immune-sites like the testicles, inside the eye and the central nervous system in people who have recovered from the disease. In women who get infected while pregnant the virus persists in the placenta, amniotic fluid and the foetus whereas for lactating mothers the virus may persist in breast milk. In this paper, an ordinary differential equation that incorporates a carrier class after disease recovery, relapse and re-infection is formulated. The model is locally asymptotically stable when the reproduction number is less than one. The models endemic equilibrium indicate that the rate of change of infection with respect to time is zero, indicating that the disease is at a constant rate in the population regulated by deaths and recoveries. Simulation results show that Ebola disease carriers can contribute greatly to the disease burden.

**Corresponding author: E-mail: achiengbrenda90@gmail.com;*

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1 Introduction

Mathematical models are instrumental in providing guidance regarding the future projections of ongoing public health crises, and in assessing the potential impact various intervention strategies may have towards the transmission control. Ebola virus is known to persist in the immune-sites like the testicles, inside the eye and the central nervous system of people who have recovered from the disease with resurgence of infections from this recoveries [1]. In women who get infected while expectant, the virus persists in the placenta, amniotic fluid and the foetus, whereas for lactating mothers the virus may persist in breast milk [1]. Currently, there is no cure for Ebola, however treatment against EVD mainly consists of providing medical care based on symptomatic therapy to maintain the vital respiratory, cardio-vascular and renal functions [2]. Several mathematical Ebola models for instance [3], [4], [5], [6], [7] among others have been developed to describe the transmission dynamics of Ebola virus.

A mathematical model which exhibits that the infection in Ebola virus is reccurent is developed in [8]. From the findings of the study, the simulation results showed that Ebola models that do not incorporate relapse and reinfection may underestimate the disease burden. The main contribution of this paper is to study the contribution of the carrier class (C) on the relapse and re-infection of transmission dynamics of Ebola virus. The paper is organized as follows; in section 2 the relapse and re-infection with carriers SEIRC model is developed and described. In section 3, positivity and boundedness of the model is studied, the basic reproduction number derived, the local stability of the disease free equilibrium and the endemic equilibrium is discussed. In section 4, the model developed in section 2 is simulated under given conditions.

2 Description and Formulation of the Model

In this section, a model is developed that subdivides the human population into classes of susceptible $S(t)$, exposed $E(t)$, infected $I(t)$, recovered $R(t)$ and carriers $C(t)$. The susceptible population is recruited at the rate Λ and are exposed at a rate β, the exposed population get infected at a rate γ, the infected individuals die as a result of infection at the rate δ and recover at the rate α, while θ represents the fraction of individuals who permanently recover from Ebola and natural death occurs in all classes at the rate μ, while π represents the rate of relapse of carriers. The total population is given by;

$$N(t) = S(t) + E(t) + I(t) + R(t) + C(t) \tag{2.1}$$

The system of differential equations describing the dynamics of the model is as follows;

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta SI - \mu S + \pi C \qquad (2.2)\\
\frac{dE}{dt} &= \beta SI - (\mu + \gamma)E\\
\frac{dI}{dt} &= \gamma E - (\mu + \delta + \alpha)I\\
\frac{dR}{dt} &= \alpha\theta I - \mu R\\
\frac{dC}{dt} &= \alpha(1-\theta)I - \mu C - \pi C
\end{aligned}$$

and takes the initial condition;

$$S(t_0) = S(0), E(t_0) = E(0), I(t_0) = I(0), R(t_0) = R(0), C(t_0) = C(0); t_0 = 0 \tag{2.3}$$

where $S(t), E(t), I(t), R(t), C(t)$ denote the susceptible, exposed, infected, recovered and carrier populations respectively.

3 Qualitative Analysis of the Model

3.1 Positivity and boundedness of solutions

Since the model describes human population, we show that the state variables of model (2.2) are non-negative and ultimately bounded in $\Gamma(\mathbb{R}^5)$.

Proposition 3.1. *Solutions of system (2.2) with initial condition (2.3) are positive for all* $t \geq 0$

Proof. To prove that for all $t \in [0, t_0]$, St, Et, It, Rt, Ct will be positive in $\Gamma(\mathbb{R}^5)$. All parameters used in the model are assumed to be positive. Taking the lower bounds in each of the equations and solving yields;

$$\begin{aligned} S(t) &\geq e^{-(\mu t+\beta I+\pi C)dt} \geq 0 \\ E(t) &\geq e^{-(\mu+\gamma)(t)} \geq 0 \\ I(t) &\geq e^{-(\mu+\delta+\alpha)(t)} \geq 0 \\ R(t) &\geq e^{-\mu t} \geq 0 \\ C(t) &\geq e^{-(\mu+\pi)(t)} \geq 0 \end{aligned} \tag{3.1}$$

Therefore for all $t \in [0, t_f]$, $S(t), E(t), I(t), R(t)$, C(t) will be positive and remain in $\mathbb{R}^5$. □

Proposition 3.2. *Solutions of system (2.2) with initial condition (2.3) are ultimately bounded.*

Proof. From Proposition (3.2) the solutions of the system (2.2) given the initial condition are ultimately bounded for all $t \geq 0$

Let $N(t) = S(t) + E(t) + I(t) + R(t) + C(t)$. From system (2.2),

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - \delta I(t) < \Lambda - \mu N(t)$$

Thus $N(t) < \frac{\Lambda}{\mu} + \epsilon$ for all large t where ϵ is an arbitrary small positive constant. Thus S(t), E(t), I(t), R(t), C(t) are ultimately bounded. □

Therefore, the model is biologically meaningful and mathematically well posed.

3.2 The basic reproduction number and equilibrium

Definition 3.1. The basic reproduction number (R_0) is the average number of secondary infections due to a single infectious individual introduced in a fully susceptible population over the course of the infectious period. If $R_0 < 1$ it means that on average, an infected individual produces less than one new infected individual while $R_0 > 1$ means each infected individual produces more than one new infection on average.

R_0 for model (2.2) is determined by the method of next generation matrix approach [9] and is given by;

$$R_0 = \frac{\beta\Lambda}{\mu(\mu+\delta+\alpha)} \tag{3.2}$$

3.3 Disease free equilibrium

A state in which no disease is present in the population. At disease free equilibrium $E = I = R = 0$.

Proposition 3.3. *For the model in system (2.2) there always exists disease free equilibrium point denoted* E_0=$(S^0, E^0, I^0, R^0, C^0) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$

3.4 The endemic equilibrium (EE)

This is a state where the disease persists in a given population. This occurs whenever R_0 is > 1. The endemic equilibrium of system (2.2) is given by;

$$E^* = (S^*, E^*, I^*, R^*, C^*)$$

Proof. To prove the existence of the endemic equilibrium, it is shown that $\frac{dI}{dt} > 0$ whenever $R_0 > 1$. From equation (3) of system (2.2);

$$\frac{dI}{dt} = \gamma E - (\mu + \delta + \alpha)I \tag{3.3}$$

but,

$$E = \frac{(\mu + \delta + \alpha)I}{\gamma} \tag{3.4}$$

Therefore substituting for E equation (3.4) into equation (3.3) yields,

$$\frac{dI}{dt} = 0 \tag{3.5}$$

□

This implies that I is a constant. Theoretically, the number of infectives in a population remains a constant this can be attributed to the to the fact that there are deaths and recoveries as much as new infections may arise.

3.5 Local stability of the DFE

The stability of equilibrium point is closely linked to the basic reproduction number (R_0) of the model under study.

Proposition 3.4. *For any time* $t \geq 0$*, the disease free equilibrium* $E_0 = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$ *of system (2.2) is asymptotically stable when* $R_0 < 1$ *and unstable when* $R_0 > 1$.

Proof. Evaluating the Jacobian matrix of system (2.2) at DFE where $E_0(S^0, E^0, I^0, R^0, C^0) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$
yields;

$$J_{DFE} = \begin{pmatrix} -\mu & 0 & -\frac{\beta\Lambda}{\mu} & 0 & \pi \\ 0 & -(\mu+\gamma) & \frac{\beta\Lambda}{\mu} & 0 & 0 \\ 0 & \gamma & -(\mu+\delta+\alpha) & 0 & 0 \\ 0 & 0 & \alpha\theta & -\mu & 0 \\ 0 & 0 & \alpha(1-\theta) & 0 & -(\mu+\pi) \end{pmatrix} \tag{3.6}$$

The eigenvalues of the matrix (3.6) are;

$$\lambda_{1,2} = -\mu$$

,

$$\lambda_3 = -(\mu + \pi)$$

To solve for the remaining eigenvalues, we study the reduced matrix;

$$J_R = \begin{pmatrix} -(\mu+\gamma) & \frac{\beta\Lambda}{\mu} \\ \gamma & -(\mu+\delta+\alpha) \end{pmatrix} \tag{3.7}$$

Whose determinant is

$$\{(\mu+\gamma)(\mu+\delta+\alpha) - \frac{\gamma\beta\Lambda}{\mu}\}$$

which can be expressed as;

$$1 - R_0 \frac{\gamma}{\mu+\gamma}$$

and trace

$$\{-(\mu+\gamma), -(\mu+\delta+\alpha)\}$$

Using the Routh Hurwitz criterion the matrix (3.7) has a negative trace and the determinant is positive if and only if $R_0 < 1$. This shows that the DFE is locally asymptotically stable whenever $R_0 < 1$. This implies that when a small number of infected individuals at class I_1 are introduced into the population, after sometime the system returns to the DFE. □

3.6 Local stability of endemic equilibrium (EE) point

Theorem 3.1. *The endemic equilibrium point E^* of system (2.2) is locally asymptotically stable if $R_0 > 1$.*

Proof. The Jacobian matrix of system (2.2) at endemic equilibrium is;

$$J_{EE} = \begin{pmatrix} -(a+\mu) & 0 & -\frac{\beta\Lambda}{\mu} & 0 & \pi \\ 0 & -(\mu+\gamma) & \frac{\beta\Lambda}{\mu} & 0 & 0 \\ 0 & \gamma & -(\mu+\delta+\alpha) & 0 & 0 \\ 0 & 0 & \alpha\theta & -\mu & 0 \\ 0 & 0 & \alpha(1-\theta) & 0 & -(\mu+\pi) \end{pmatrix} \tag{3.8}$$

where $a = \beta I$. From matrix (3.8) the diagonal elements are negative. The eigenvalues of any square matrix say b are equal to those of B^T. Matrix (3.8) is stable if it is diagonally dominant in columns. Set $\phi = max\{b_1, b_2, b_3, b_4, b_5\}$ where;

$$\begin{aligned} b_1 &= |-a-\mu| > |a| \\ b_2 &= |-(\mu+\gamma)| > |\gamma| \\ b_3 &= |-(\mu+\delta+\alpha)| > |-\frac{\beta\Lambda}{\mu} + -\frac{\beta\Lambda}{\mu} + \alpha\theta + \alpha(1-\theta)| \\ b_4 &= |-\mu| > 0 \\ b_5 &= |-(\mu+\pi)| > |\pi| \end{aligned} \tag{3.9}$$

which indicates that matrix (3.8) is diagonally dominant in columns, then by the Gershgorin disc argument [10], the eigenvalues of matrix (3.8) lie within atleast one Gershgorin disc. □

Therefore the endemic equilibrium is locally asymptotically stable whenever $R_0 > 1$. Epidemiologically, introducing a small number of infected individuals into a susceptible population, each infected individual will produce more than one secondary infection on average in the entire infectious period.

4 Numerical Values and Analysis

Matlab software was used to illustrate the numerical results describing the theoretical results for system (2.2). The parameters used in the simulation are either obtained from literature or estimated. The parameter values have been varied to better understand the role of carriers in disease relapse and re-infection.

Table 1. Parameter values used in simulation

Parameters	Description	Range	Source
β	Infection rate	0.02×10^{-6}	Varies
θ	Fraction acquiring immunity	0.8	Varies
π	Relapse rate of the susceptible	0.9	Estimated
μ	Natural death rate	$[0, 1]day^{-1}$	[2]
δ	Disease induced death rate	$[0.5]day^{-1}$	[6]
α	Recovery rate	(0.7-0.9)	Varies
$\frac{1}{\gamma}$	Incubation period	1 week	

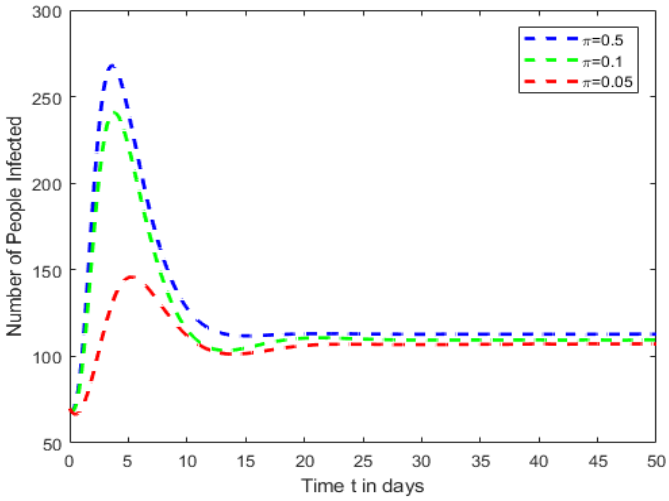

Fig. 1. Impact of Carriers on the number of Infections

Fig. 1 illustrates the impact of carriers on the infected class. With a small percentage of carriers relapsing ($\pi = 0.05$) the infected population peaks at 150 infections, where as with ($\pi = 0.5$) the infected population peaks at approximately 270 infections.

With ($\pi = 0.05, 0.1, 0.5$), the susceptibles drop at a sharp rate to the exposed class as shown in Fig. 2. This implies that regardless of the number of carriers relapsing, the susceptibles are affected greatly.

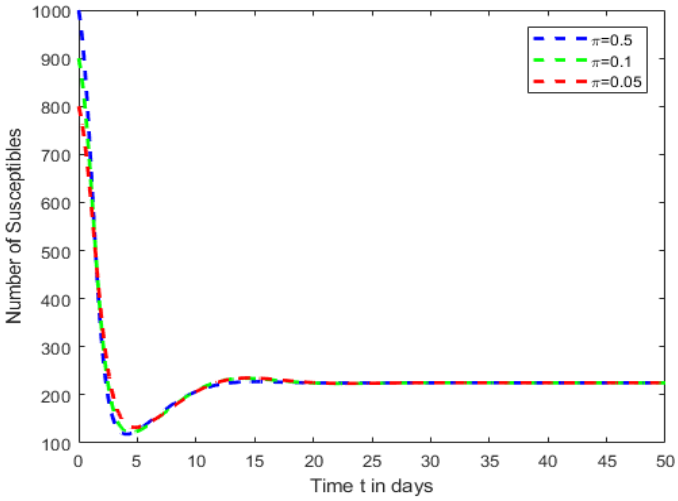

Fig. 2. Impact of Carriers on the Susceptibles

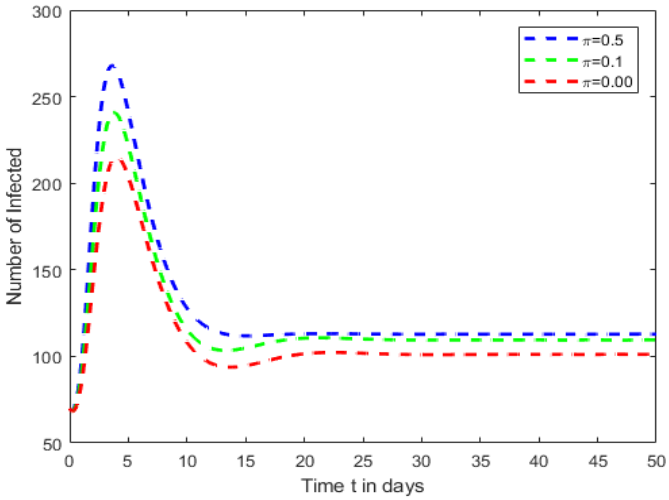

Fig. 3. Impact of Carriers on the number of Infections when ($\pi = 0$)

In Fig. 3 when $\pi = \theta = 0$, the system (2) reduces to an SEIR model which illustrates number of infections arising from a new disease episode without carriers relapsing and re-infection.

5 Discussion

An EVD outbreak can occur in a large magnitude and overwhelm the fragile health systems of the affected countries. Local and international agencies efforts to create response on patient care and interruption of transmission have still not brought the epidemic to a halt, with recurrences being observed. Short incubation periods of EVD are likely due to exposure to highly contaminated materials. The risk of EVD infection is considered very low if appropriate infection prevention and control precautions are strictly followed and also not considered contagious before initial onset of symptoms. The existence of the endemic equilibrium shows that with the carrier class the infection is constantly in the population with stability analysis indicating that the model is locally stable. The numerical simulation of the model demonstrates that carriers of Ebola virus have a significant impact on the relapse and re-infection of the disease.

6 Conclusion

The 2014 EVD outbreak in West Africa attracted global attention due to the high incidence and mortality rates as well as potential of international spread of the virus as a result of human travel. The disease has kept on recurring and therefore there is need to assess new dimensions on how to control future outbreaks. In this paper, a new class of carriers for Ebola virus disease was introduced to determine their impact on relapse, reinfection and recurrence of the disease. The results in this paper extend the existing studies on Ebola Virus.

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Competing Interests

Author has declared that no competing interests exist.

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