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Mathematical Model for Ebola Virus Infection in Human with Effectiveness of Drug Usage

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ABSTRACT: In this paper, we formulated a mathematical model of the dynamics of Ebola virus infection incorporating effectiveness of drug usage. The infection free and infection persistence equilibrium points were obtained. The control reproduction number was obtained which was used to analyse the local and global stability of the infection-free equilibrium. Using the method of linearization, the infection-free equilibrium (IFE) state was found to be locally asymptotically stable if $R_c < 1$ and unstable if $R_c > 1$. By constructing lyapunov function, the infection-free equilibrium was found to be globally asymptotically unstable if $R_c > 1$. Numerical simulation of the model was done. It is observed that, as percentage of effectiveness of drug administration increases, the control reproduction number decreases. This suggests that with the help of drugs usage, the immunes system have the ability to suppress the increase of infected cells, as well as virus load which shown that the virus does not maintain an infection in the system.

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Ebola virus is a highly infectious and deadly (lethal) disease. The virus is among the most dangerous and devastating threats to human health, causing a large number of fatalities. The virus was first discovered in 1976 in Democratic Republic of Congo (Fritz, 2012). Recently, the virus again resurfaced in some West African Countries like Guinea, Sierra Leone, Liberia and Nigeria. The incubation period of Ebola virus ranges from 2 to 21 days and infectious period ranges from 4 to 10 days (WHO, 2014). Meanwhile, it takes an approximation of 31 days to quarantine a patient under investigation of the Ebola virus. Consequently, the symptoms of the Ebola virus are characterized by headaches, fever, vomiting, bleeding diarrhoea, and rash (Fauci, 2014), in infected person, severe bleeding and shock are usually followed by death. The spread of the virus and eventual death of infected patients was largely contained (reduced) through early detection and effective contact tracing (Beeching *et al.*, 2014).

Ebola virus is known to cause damage to large variety of cell types including monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes, and several types of epithelial cells. The primary targets of the virus are dendritic, monocytes and macrophage cells (Centre for Disease Control and Prevention (CDC), 2014). Mathematical models have played a key role in the formulation of the dynamics of Ebola virus infectious and control strategies for non-immune response (Chowell *et al.*, 2015). Mathematical models have played a central role to capture the dynamics of different virus infection (Chowell *et al.*, 2015). The model equations are formulated using ordinary differential equation. The aim of this paper is therefore to formulate a mathematical model of the dynamics of Ebola virus infection in the cell population and immune response by incorporating effectiveness of drug usage, humoral immunity and clearance of the free virus.

MATERIALS AND METHODS

Model Formulation: The human cell population is divided into the following classes: uninfected cells (U), infected cell (I), free virus (V), cytotoxic T-lymphocyte (T) and B-cell (Antibody) (B). Thus, the model indicates the passage of individuals cell is from the virus class, V, infect uninfected class, U, to progress to infected class, I and move back to free virus class for more viruses to be produced in the absence of immune response. Cytotoxic T-lymphocyte class, T, interact with infected cells for the purpose of wipe out the infected cells. The B-cells (Antibody) class, B, interact with the free virus and neutralized the free virus from the system. The uninfected cell

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population increase by production rate β and having death rate μ_1. When a free virus infect the U(t) population and produced infected cells at rate α and with death rate μ_2. Infected cells move to free virus class at rate ω and die at rate μ_3. T(t) population increase by rate γ, boosted at rate k_1, kill infected cells at rate δ_1 and die at rate μ_4. B(t) class produced at rate θ, boosted at rate k_2, neutralized the free virus at rate δ_2 and μ_5 is the death rate of B(t). The effectiveness of the drug in blocking production of infectious virus, ϕ. The effect of ϕ is to reduce the production of infected cells, we have the range of effectiveness of drug usage as $0 \le \phi \le 1$ thus it measure of its efficacy, if $\phi = 1$ it is completely effective and prevents all production of infected cells, while $\phi = 0$ it implies that there is no drug and control intervention against the Ebola virus infection. This model explores the effect of drugs usage on the Ebola virus.

Table 1: Parameters of the Model

Parameters	Description
β	Reproduction rate of uninfected cell
α	Infection rate of uninfected cell
ω	Reproduction rate of Virus
γ	Reproduction rate of Cytotoxic T-cells
θ	Reproduction rate of antibodies
δ_1	Clearance rate of infected cells
δ_2	Clearance rate of the viruses by antibodies
μ_1	Natural death rate of uninfected cell
μ_2	Death rate of infected cell
μ_3	Decay rate of the virus
μ_4	Death rate of Cytotoxic T-cell
μ_5	Death rate of B-cell secreted antibodies
k_1	Booster of CTL
k_2	Booster of Antibody
$\emptyset$	Effectiveness of drug usage

The corresponding mathematical equations of the above description are given by a system of ordinary equations below:

$$\frac{dU}{dt} = \beta - \mu_1 U - (1-\phi)\alpha UV \qquad (1)$$

$$\frac{dI}{dt} = (1-\phi)\alpha UV - \mu_2 I - \delta_1 IT \qquad (2)$$

$$\frac{dV}{dt} = \omega I - \mu_3 V - \delta_2 BV \qquad (3)$$

$$\frac{dT}{dt} = k_1 T + \gamma T - \mu_4 T \qquad (4)$$

$$\frac{dB}{dt} = k_2 B + \theta BV - \mu_5 B \qquad (5)$$

ANALYSIS OF THE MODEL

Equilibrium States of the Model: At equilibrium states,

$$\frac{dU}{dt} = \frac{dI}{dt} = \frac{dV}{dt} = \frac{dT}{dt} = \frac{dB}{dt} = 0 \qquad (6)$$

Therefore, Infection Free equilibrium (IFE) denoted as

$$E_0 = (U^0,\ I^0,\ V^0,\ T^0,\ B^0) = \left(\frac{\beta}{\mu_1},\ 0,\ 0,\ 0,\ 0\right) \qquad (7)$$

Control Reproductive Number, R_c: To derive the control reproductive number of Model (1)-(5), we first introduce the method of next generation matrix formulated by (Diekmann and Heesterbeek, 2000; Driessche Van den and Watmough, 2002). Therefore, we have the following

$$F = \begin{pmatrix} 0 & (1-\phi)\alpha U^0 \\ \omega & 0 \end{pmatrix} \qquad (8)$$

$$V = \begin{pmatrix} \mu_2 + \delta_1 T^0 & 0 \\ 0 & \mu_3 + \delta_2 B^0 \end{pmatrix} \qquad (9)$$

The inverse of (9) gives

$$V^{-1} = \frac{1}{(\mu_2 + \delta_1 T^0)(\mu_3 + \delta_2 B^0)} \begin{pmatrix} (\mu_3 + \delta_2 B^0) & 0 \\ 0 & (\mu_2 + \delta_1 T^0) \end{pmatrix} \qquad (10)$$

The multiplication of (8) and (10) give

$$FV^{-1} = \begin{pmatrix} 0 & (1-\phi)\alpha \dfrac{\beta}{\mu_1(\mu_3 + \delta_2 B^0)} \\ \dfrac{\omega}{(\mu_2 + \delta_1 T^0)} & 0 \end{pmatrix} \qquad (11)$$

The characteristics equation of (11) gives

$$\left|(FV^{-1}) - \lambda\right| = \begin{vmatrix} -\lambda & (1-\phi)\alpha \dfrac{\beta}{\mu_1(\mu_3 + \delta_2 B^0)} \\ \dfrac{\omega}{(\mu_2 + \delta_1 T^0)} & -\lambda \end{vmatrix} = 0 \qquad (12)$$

Determinant of (12) gives

$$\lambda = \sqrt{\frac{\omega(1-\phi)\alpha\beta}{(\mu_2 + \delta_1 T^0)\mu_1(\mu_3 + \delta_2 B^0)}} \qquad (13)$$

λ is the largest eigenvalue which is spectral radius of $e(FV^{-1})$. Therefore, the control reproductive number is

$$R_c = \sqrt{\frac{\omega(1-\phi)\alpha\beta}{(\mu_2 + \delta_1 T^0)\mu_1(\mu_3 + \delta_2 B^0)}} \qquad (14)$$

Thus, the equation (14) is the control reproductive number of the system (1)-(5).

LOCAL STABILITY OF INFECTION FREE EQUILIBRIUM (E^0)

Theorem 1: The Infection Free Equilibrium (IFE) of the model equations (1) - (5) is local asymptotically stable if $R_c < 1$

Proof:

$J(E^0) = (U^0, I^0, V^0, T^0, B^0) =$

$$J(E_0) = \begin{pmatrix} -\mu_1 - (1-\phi)\alpha V & 0 & -(1-\phi)\alpha U & 0 & 0 \\ (1-\phi)\alpha V & (-\mu_2 - \delta_1 T) & (1-\phi)\alpha U & -\delta_1 I & 0 \\ 0 & \omega & (-\mu_3 - \delta_2 B) & 0 & -\delta_2 V \\ 0 & \gamma T & 0 & (k_1 + \gamma I - \mu_4) & 0 \\ 0 & 0 & \theta B & 0 & (k_2 + \theta B - \mu_5) \end{pmatrix} \quad (15)$$

$$J(E_0) = \begin{pmatrix} -\mu_1 & 0 & -(1-\phi)\alpha \frac{\beta}{\mu_1} & 0 & 0 \\ 0 & -\mu_2 & (1-\phi)\alpha \frac{\beta}{\mu_1} & 0 & 0 \\ 0 & \omega & -\mu_3 & 0 & 0 \\ 0 & 0 & 0 & (k_1 - \mu_4) & 0 \\ 0 & 0 & 0 & 0 & (k_2 - \mu_5) \end{pmatrix} \quad (16)$$

Using Gaussian elimination row operation on (16) gives

$J(E^0) = (\frac{\beta}{\mu_1}, 0, 0, 0, 0)$

$$\begin{pmatrix} -\mu_1 & -(1-\phi)\alpha \frac{\beta}{\mu_1} & 0 & 0 & 0 \\ 0 & (1-\phi)\alpha \frac{\beta}{\mu_1} & 0 & 0 & 0 \\ 0 & 0 & \frac{(1-\phi)\alpha \frac{\beta}{\mu_1}\omega}{(-\mu_3 - \delta_2 B^0)} - (-\mu_2 - \delta_1 T^0) & 0 & 0 \\ 0 & 0 & 0 & k_1 - \mu_4 & 0 \\ 0 & 0 & 0 & 0 & (k_2 - \mu_5) \end{pmatrix} \quad (17)$$

Thus, the characteristic equation of (17) is $\left|J(E^0) - \lambda \mathrm{I}\right| = 0$, implies,

$$\begin{vmatrix} (-\mu_1) - \lambda & -(1-\phi)\alpha \frac{\beta}{\mu_1} & 0 & 0 & 0 \\ 0 & ((1-\phi)\alpha \frac{\beta}{\mu_1}) - \lambda & 0 & 0 & 0 \\ 0 & 0 & \frac{(1-\phi)\alpha\beta\omega}{\mu_1(-\mu_3 - \delta_2 B^0)} - (-\mu_2 - \delta_1 T^0) - \lambda & 0 & 0 \\ 0 & 0 & 0 & (k_1 - \mu_4) - \lambda & 0 \\ 0 & 0 & 0 & 0 & (k_2 - \mu_5) - \lambda \end{vmatrix} = 0 \quad (18)$$

$$\lambda_1 = -\mu_1 < 0 \quad (19)$$

$$\lambda_2 = (1-\phi)\alpha \frac{\beta}{\mu_1}, \quad (20)$$

The IFE will be asymptotically stable if,

$$\lambda_2 < 0 \quad (21)$$

This implies that,

$$(1-\phi)\alpha\beta < \mu_1 \quad (22)$$

$$\lambda_3 = \frac{(1-\phi)\alpha\beta\omega}{\mu_1(-\mu_3 - \delta_2 B^0)} - \mu_2 - \delta_1 T^0 \quad (23)$$

Simplification of (23) gives,

$$\frac{(1-\phi)\alpha\beta\omega - \mu_1(-\mu_3 - \delta_2 B^0)(-\mu_2 - \delta_1 T^0)}{\mu_1(-\mu_3 - \delta_2 B^0)} < 0 \quad (24)$$

$$\frac{(1-\phi)\alpha\beta\omega}{\mu_1(-\mu_3 - \delta_2 B^0)} - \frac{\mu_1(-\mu_3 - \delta_2 B^0)(-\mu_2 - \delta_1 T^0)}{\mu_1(-\mu_3 - \delta_2 B^0)} < 0 \quad (25)$$

Implies,

$$\frac{(1-\phi)\alpha\beta\omega}{\mu_1(-\mu_3 - \delta_2 B^0)(-\mu_2 - \delta_1 T^0)} - \frac{\mu_1(-\mu_3 - \delta_2 B^0)}{\mu_1(-\mu_3 - \delta_2 B^0)} < 0 \quad (26)$$

Therefore, we have

$$R_c^2 - 1 < 0 \quad (27)$$

$$R_c^2 < 1 \quad (28)$$

$$\lambda_4 < 0 \; if \; \mu_4 > k_2 \quad (29)$$

$$\lambda_5 < 0 \; if \; \mu_5 > k_2 \quad (30)$$

Thus, the infection-free equilibrium, E^0 of (1)-(5) is locally asymptotically stable if $R_c < 1$. Hence the epidemiological implications of the theorem is that Ebola virus may be control or eradicated from cell population when $R_c < 1$.

GLOBAL STABILITY OF IFE **(E^0):** We used Lyapunov function to investigate the stability of the infection free equilibrium,

Theorem 2: The Infection Free Equilibrium, E^0 of (1) - (5) is globally asymptotically stable (GAS) if $R_c \leq 1$

Proof: To establish the global stability of the infection free equilibrium, we select the infected classes for construction of Lyapunov function. We have

$$L(I,V) = (\mu_3 + \delta_2 B)I + (1-\emptyset)\alpha UV \quad (31)$$

as a good candidate for a Lyapunov function and must satisfied

$$\dot{L}(I,V) \leq 0 \text{ for } R_c \leq 1 \quad (32)$$

We take derivative of (31) gives

$$\dot{L}(I,V) = (\mu_3 + \delta_2 B)\dot{I} + (1-\emptyset)\alpha U\dot{V} \quad (33)$$

We substitute for $\dot{I}$ and $\dot{V}$ from equations (2) and (3) into equation (33), we have,

$$\dot{L}(I,V) = (\mu_3 + \delta_2 B)((1-\emptyset)\alpha U.V - \mu_2 I - \delta_1 \mathrm{I}.T) + (1-\emptyset)\alpha U(\omega \mathrm{I} - \mu_3 V - \delta_2 B.V) \quad (34)$$

Gives

$$\dot{L}(I,V) = (1-\emptyset)\alpha U.V(\mu_3 + \delta_2 B) + (-\mu_2 I - \delta_1 \mathrm{I}.T)(\mu_3 + \delta_2 B) + (1-\emptyset)\alpha U(\omega \mathrm{I}) - (1-\emptyset)\alpha U(\mu_3 V + \delta_2 B.V) \quad (35)$$

$$\dot{L}(I,V) = (1-\emptyset)\alpha U.V(\mu_3 + \delta_2 B) - (1-\emptyset)\alpha U(\mu_3 V + \delta_2 B.V) + \{(-\mu_2 - \delta_1 T)(\mu_3 + \delta_2 B) + (1-\emptyset)\alpha U\omega\}\mathrm{I} \quad (36)$$

Equation (36) reduced to, $\dot{L}(I,V) = \{(-\mu_2 - \delta_1 T)(\mu_3 + \delta_2 B) + (1-\emptyset)\alpha U\omega\}\mathrm{I}$ (37)

Implies,

$$\dot{L}(I,V) = \{(1-\emptyset)\alpha U^0\omega - (\mu_2 + \delta_1 T^0)(\mu_3 + \delta_2 B^0)\}\mathrm{I} \quad (38)$$

At the infection-free equilibrium state, equation (38) gives,

$$\dot{L}(I,V) = \{\frac{(1-\emptyset)\alpha\beta\omega}{\mu_1} - (\mu_2 + \delta_1 T^0)(\mu_3 + \delta_2 B^0)\}\mathrm{I} \quad (39)$$

From (39), we have

$$\dot{L}(I,V) = (\mu_2 + \delta_1 T^0)(\mu_3 + \delta_2 B^0)\{\frac{(1-\emptyset)\alpha\beta\omega}{(\mu_2+\delta_1 T^0)(\mu_3+\delta_2 B^0)\mu_1} - 1\}\mathrm{I} \quad (40)$$

then we have,

$$\dot{L}(I,V) = (\mu_2 + \delta_1 T^0)(\mu_3 + \delta_2 B^0)\mathrm{I}\{R_c^2 - 1\} \quad (41)$$

Hence, we have

$$\dot{L}(I,V) \leq 0 \quad (42)$$

$$if \ R_c^2 \leq 1 \text{ then } R_0 \leq 1 \quad (43)$$

The infection-free equilibrium is globally asymptotically stable (GAS) if $R_c \leq 1$

INFECTION PERSISTENCE EQUILIBRIUM

Let $E_1 = (U, I, V, T, B) = (U^{**}, I^{**}, V^{**}, T^{**}, B^{**})$

be an infection persistence equilibrium point, equation (1) to (5) becomes

$$\beta - \mu_1 U^{**} - (1-\phi)\alpha U^{**}V^{**} = 0 \quad (44)$$

$$(1-\phi)\alpha U^{**}V^{**} - \mu_2 I^{**} - \delta_1 I^{**}T^{**} = 0 \quad (45)$$

$$\omega I^{**} - \mu_3 V^{**} - \delta_2 B^{**}V^{**} = 0 \quad (46)$$

$$k_1 T^{**} + \gamma I^{**}T^{**} - \mu_4 T^{**} = 0 \quad (47)$$

$$k_2 B^{**} + \theta B^{**}V^{**} - \mu_5 B^{**} = 0 \quad (48)$$

From (48) and (44) we have

$$U^{**} = \frac{\beta\theta}{\theta\mu_1 + (1-\phi)\alpha(\mu_5 - k_2)} \quad (49)$$

From (46), (47), (48) with (45), we have

$$T^{**} = \frac{\alpha\gamma\beta(1-\phi)(\mu_5 - k_2) - \mu_2(\mu_4 - k_1)(\theta\mu_1 + (1-\phi)\alpha(\mu_5 - k_2))}{(\delta_1(\mu_4 - k_1)(\theta\mu_1 + (1-\phi)\alpha(\mu_5 - k_2))} \quad (50)$$

From (44)-(48), we have

$$B^{**} = \frac{\omega\theta(\mu_4 - k_1) - \gamma\mu_3(\mu_5 - k_2)}{\delta_2\gamma(\mu_5 - k_2)} \tag{51}$$

Therefore, Infection Persistence Equilibrium (IPE) denoted as

$$E_1 = (U^{**},\ I^{**},\ V^{**},\ T^{**},\ B^{**}) = \begin{pmatrix} \frac{\beta\theta}{\theta\mu_1 + (1-\phi)\alpha(\mu_5 - k_2)} \\ \frac{\mu_4 - k_1}{\gamma} \\ \frac{\mu_5 - k_2}{\theta} \\ \frac{\alpha\gamma\beta(1-\phi)(\mu_5 - k_2) - \mu_2(\mu_4 - k_1)(\theta\mu_1 + (1-\phi)\alpha(\mu_5 - k_2))}{(\delta_1(\mu_4 - k_1)(\theta\mu_1 + (1-\phi)\alpha(\mu_5 - k_2))}, \\ \frac{\omega\theta(\mu_4 - k_1) - \gamma\mu_3(\mu_5 - k_2)}{\delta_2\gamma(\mu_5 - k_2)} \end{pmatrix} \tag{52}$$

RESULTS AND DISCUSSION

Numerical simulations of the model: For the purpose of model validation, in order to ensure that the model is in agreement with reality, numerical simulation is undertaking using the data provided in Table 2. The results are displayed in Figure 1 to Figure 4. Figure 1 and Figure 2 shown that, as effectiveness of drug administration increases its percentage, it decrease the control reproduction number. In Figure 3, it is observed that, as percentage of effectiveness of drug usage increases, the control reproduction number decreases. This shown that an infection does not have the ability to established itself. Figure 4, shown that, as death rate of infected cells increases the control reproduction number decreases.

Table 2: Values for Parameters of the Model

Parameter	Value	Source
β	5.05cells/ml/day	Wester, 2015
α	0.1cell/ml/day	CDC, 2014
ω	40.9	Wester, 2015
γ	0.1ml/cell/day	Banton *et al.*, 2010
θ	0.1cell/day	Assumed
δ_1	0.1cell/day	Wester, 2015
δ_2	0.1cell/day	Assumed
μ_1	0.03cell/day	Wester, 2015
μ_2	0.5cell/day	Assumed
μ_3	1.15cell/day	Nguyen *et al.*, 2015
μ_4	0.5cell/day	Wester, 2015
μ_5	0.02cell/day	Assumed
$\emptyset$	$0 < \emptyset < 1$	Assumed
k_1	0.25	Assumed
k_2	0.25	Assumed

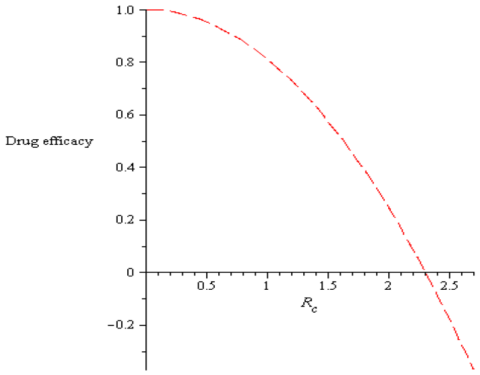

Fig 1: Effect of Drug efficacy on the control reproduction number

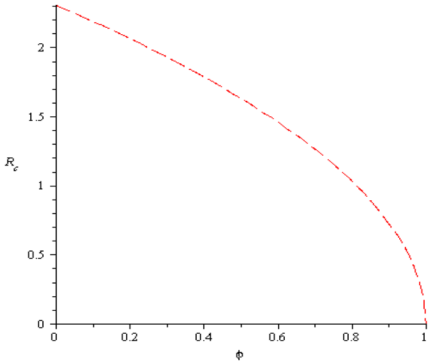

Fig 2: Effect of Drug efficacy on the control reproduction number

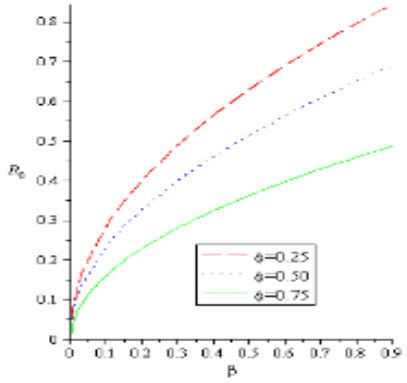

Fig 3: Effect of production rate of U(t) on control reproduction number varying Ø and death rate of infected cells on $\boldsymbol{R_c}$

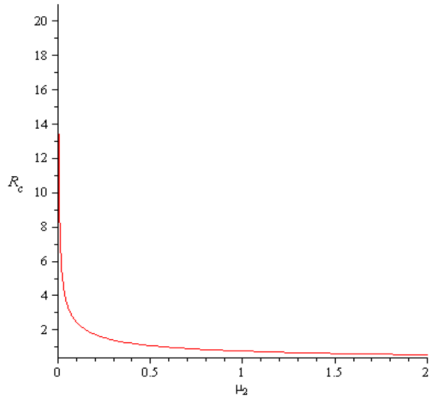

Fig 4: Effect of production rate of U(t) on control reproduction number varying Ø and death rate of infected cells on $\boldsymbol{R_c}$

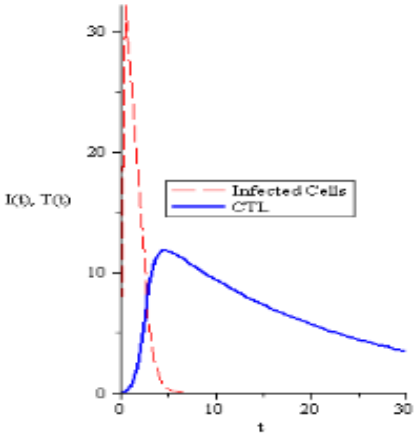

Fig 5: The relationship between the infected cells, CTLs against time and between the viruses, antibody against time.

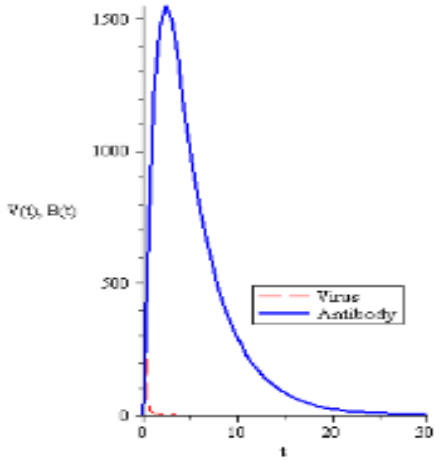

Fig 6: The relationship between the infected cells, CTLs against time and between the viruses, antibody against time

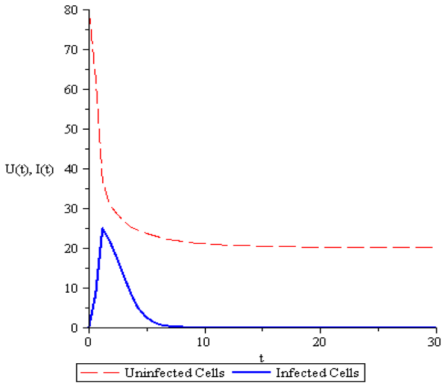

Fig7: The relationship between the uninfected cells, infected cells against time

The infection will die out of the system as effort is made to control the infection. Figures 7-8 shown that upon introduction of the virus, the population of uninfected cells decreases relative to the infected cells population, this behavior continues until the virus reaches the peak infected cells point. After reaching this value, the infected cells population begins to decline until it reaches zero. This suggests that with the help of drugs usage, the immunes system have the ability to suppress the increase in infected cells, as well as virus load which shows that the virus does not maintain an infection in the system.

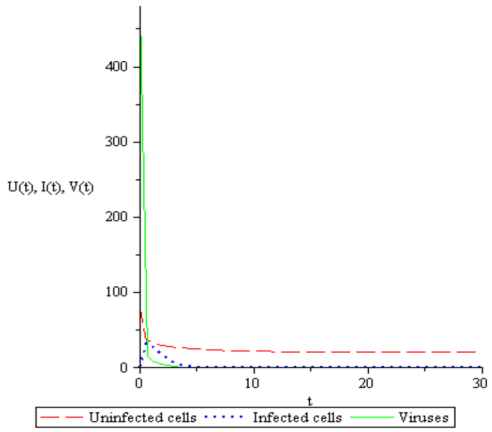

Fig 8: The relationship between the uninfected cells, infected cells against time

*Conclusion***:** In this paper, we developed, analyzed and study effectiveness of drug usage on the dynamics of Ebola virus infection in human cells population. The infection free and infection persistence equilibria were obtained and investigated. The model showed that the infection free equilibrium is locally asymptotically stable $\boldsymbol{R_c < 1}$ and unstable at threshold parameter greater than a unit. While the infection free equilibrium with method of Lyapunov function is globally asymptotically unstable if the threshold parameter is greater than a unit. Finally there is a need for further research work on the age of infection on dynamics of Ebola virus infection.

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