Journal of Medical Sciences

ISSN 1682-4474

Research Paper

J. Med. Sci., 15 (4): 160-177
15th May, 2015
DOI: 10.3923/jms.2015.160.177

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

For further information about this article or if you need reprints, please contact:

Hawa Adusei
Department of Mathematics,
Kwame Nkrumah University of Science and Technology,
Kumasi, Ghana
Tel : +233243412811

Mathematical Model of the Behaviour of T Cytotoxic, T Helper, B and Natural Killer Cells in the Presence of Viruses

[1]Hawa Adusei, [2]M.T. Agyei Frempong,
[1]Kwaku Darkwah and [1]Emmanuel Osei-Frimpong

The behaviour of lymphoid cells in the absence of viruses has already been published in the year 2013. This study is a continuation of recent attempts to understand, via mathematical modeling, the behavior of lymphoid cells in the absence and in the presence of viruses. In this study, which is the behaviour of lymphoid cells in the presence of viruses will be treated in three respects. Firstly, the innate immune response stage, secondly, the overlap of innate and adaptive immune responses stage and finally, the adaptive immune response stage of viral infections. The adaptive immune response stage considers the viremia and cell-mediated immune responses stage. The steady states and the stability for these differential models are deduced. Each of the models permit the existence of two types of stationary states. There is the state of no infection, with no virus cells while the other is the state of co-existence where a virus cell persists against the background of immune response. The state of no infection is asymptotically stable and a state of infection is unstable. It is found from the study that the state of no infection represents the preparedness of the immune state prior to the infection. Numerical simulation analysis suggests that the cells (NK, T_c, T_h and B) grow exponentially as a result of proliferation and saturation because of the contacts between them and reach therefore reach plateau as time (t) increases. These immune cells are able to reduce viral load to the barest minimum if not reducing it to zero.

Key words: Innate and adaptive immune responses, lymphocytes, viral infections, mathematics modeling and stability analysis

[1]Department of Mathematics, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana
[2]School of Medical Science, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

ANSInet
Asian Network for Scientific Information

INTRODUCTION

Infectious diseases are the second leading cause of death among humans worldwide, but number one cause of death in developing countries (Heffernan *et al*., 2009). The practical importance of understanding the dynamics and evolution of infectious diseases and specifically viral infection is steadily increasing in the contemporary world (Iwasa *et al*., 2007). This study is rich with epidemiological models, which have greatly added to our understanding of outbreaks, epidemics and pandemics of diverse pathogens. Generally, diseases transmitted by viral agents, such as influenza, measles, rubella (German measles) and chicken pox, confer immunity against reinfection, while diseases transmitted by some bacteria, such as tuberculosis, meningitis and gonorrhea, confer only partial immunity against reinfection (Brauer, 1984).

Resistance is better known as immunity. The immune system is the body's defense mechanism against infectious diseases. The immune system includes the organs, tissues, cells and molecules responsible for immunity. There are two types of immunity. The first is innate (natural or native or nonspecific) which refers to the basic resistance to disease that an individual is born with. The second one is the specific or acquired or adaptive immunity which requires the activity of a functional immune system involving cells called lymphocytes and their products (Nirvanagrewal, 2012).

Innate defense mechanisms provide the first line of host defense against invading pathogens until an acquired immune response develops. The interaction between the pathogen and the components of innate immunity triggers generation of an adaptive immune response that usually consists of pathogen-specific cytotoxic T cells (CTLs) and antibody molecules produced by B cells (Heffernan *et al*., 2009).

Acquired or adaptive or specific immunity reflects the presence of a functional immune system that is capable of specifically recognizing and selectively eliminating foreign microorganisms. T cells, B cells and natural killer cells play an important role in immunity against viral infections. T cells have been divided into two major subsets that are functionally and genetically different.

T helper cells ($CD4^+$ T cells) which function to mediate responses by the secretions of lymphokines that stimulate other cells involved in the immune responses. The second subset are cytotoxic T cells ($CD8^+$ cells) and these cells are directly involved in the killing of certain tumor cells, virus infected cells, transplant cells and sometimes eukaryotic parasites. The $CD8^+$ T cells are also important in down regulation of immune responses. In this case, they are referred to as T suppressor cells. Natural killer cells are similar to the $CD8^+$ T cells. They function as effector cells that directly kill certain tumor cells and virus infected cells. When the innate immune response fails to control the infection, the adaptive immune response is activated and this involves the production of antibodies and primed T cells. The $CD8^+$ cytotoxic T lymphocytes (CTLs) kill target cells infected with viruses or bacteria. The $CD4^+$ T-helper (Th1) cells provide help for B cells to develop into antibody secreting plasma cells following stimulation by foreign antigens such as bacteria antigen and tumor cells. Antibodies are specialized proteins that specifically recognize and bind to specific antigens that call their stimulation. Antibody production and binding to foreign antigen is often critical as a means of signaling other cells to engulf, kill or remove that substance from the body. Antibody production and secretion of cytokines that play a role in immune-regulatory functions or have a direct effect on invading pathogens (Germain, 1994). Human immune response to viral infections is caused by a variety of cells in the innate and adaptive mechanisms (Baron, 1996). Many different population growth models have been used for modeling disease progress curves. The logistic model has many real world applications in biology, ecology, statistics, neural networks, reaction models (chemistry), Fermi distribution (physics) and in medicine. Logistic growth model has been assumed in many epidemic models where population growth is limited (Ackleh and Allen, 2003). The main point about the logistic model is that it is a particularly convenient form to take when seeking for qualitative dynamic behaviour in populations (Murray, 2001).

Mathematical modeling using differential equations and dynamical systems have been used in the studies of immune response to various infections, most notably that of the HIV. The question now is how does the human body develop immunity or immune response to these infectious diseases such as viruses? The mathematical biologists Anderson and May (1992) proposed a theory and a mathematical model to explain this phenomenon. Bittner and Wahl (2000) studied the immune response against conserved and variable viral epitopes. The main immune cell studied was cytotoxic T lymphocytes. Wodarz (2004) reported on mathematical models which have investigated the importance of lytic and non-lytic immune responses for the control of viral infections. Lytic immune responses fight the virus by killing infected cells, while non-lytic immune responses fight the virus by inhibiting viral replication. All these researchers have not dealt with the behavior of these lymphoid cells which fight the viruses. Wodarz *et al*. (2007) published a study on the dynamics of killer T cell inflation in viral infections in which authors analyzed the impact of innate and adaptive immune responses. According to the study of these authors, a potentially contributor to cytotoxic T lymphocytes inflation is a competition between the specific cytotoxic T lymphocytes response and an innate Natural Killer (NK) cell response. Hancioglu *et al*. (2007), presented a simplified dynamical model of immune response to uncomplicated Influenza A Virus (IAV) infection which focuses on the control of the infection by the innate and adaptive immunity. Long *et al*. (2008), also worked on a Mathematical Modeling of Cytotoxic

Lymphocyte-Mediated Immune Response to Hepatitis B Virus Infection in which the Human Immunodeficiency Virus (HIV) infection was successfully to simulate the interaction between HIV and cytotoxic lymphocyte mediated immune response and also considered the indicator of the liver cell damage between Hepatitis B and the cytotoxic mediated immune response and the indicator of the liver cell damage. Wiah *et al*. (2011) presented a mathematical model of immune response to Hepatitis B Virus (HBV) infection which focuses on the control of the infection by the interferons, innate and adaptive immunity. Nakata (2011) published study on the global dynamics of a cell mediated immunity in viral infection models with distributed delays which admitted three possible equilibria states. Pawelek (2012), also published a study on the mathematical modeling of virus infections and immune responses in which HIV infection was considered. The author of this study examined the relative roles of target cell availability and innate and adaptive immune responses in controlling the viruses. In addition, the study of Pawelek (2012), provided a quantitative understanding of the biological factors which could explain the viral and interferon kinetics during a typical influenza virus infection. Ben-Shachar and Koelle (2014) also published a study on Minimal within-host dengue models which highlights the specific roles of the immune response in primary and secondary dengue infections. Tian and Wang (2015) published a study on the stability and analysis for viral infections which focused on humoral immunity.

These authors dealt with specific viral infections and therefore do not seem to continue with the work of Anderson and May (1992). This current study seeks to modify the work of Anderson and May (1992) which consisted of the behaviour of two effector cells (T and B lymphocytes) in the presence of viruses. Anderson and May (1992) considered the adaptive stage of virus clearance. This study seeks to extend it by including the dynamics of two effector cells (Natural Killer cells and T helper cells) and also to consider the innate immune response stage where these NK cells provide the first line of defense to viral infections. The study also seeks to consider an overlap of the innate and adaptive immune responses of these effector cells to the viral infection and finally consider the adaptive stage which also has two sub-divisions thus viremia stage and cell-mediated immune responses.

MATERIALS AND METHODS

The model is developed in four stages as the innate immune response stage, the overlap of innate and adaptive immune responses stage, the viremia stage of viral clearance and finally the cell-mediated adaptive immune response stage. The model of the study contains five variables and these are Natural killer cells (N), Cytotoxic T cells (T_c) T helper cells (T_h) and B lymphocytes (B). The assumptions of the mathematical model as well as certain parameter values are borrowed from the dynamics and data provided in the study of Anderson and May (1992). The constants reproduction rates, the self-reproduction rate, death rates and the rate at which the immune cells and the viruses interact to saturate are considered in the models, the equilibrium points and their stability for the system of the extended differential equations are analyzed and the stability of the linearized equations is determined. Time histories of these systems of differential equations are also used to analyze the systems. Phase portrait is drawn to show the interaction between the T cells and the virus cells. Parameter values which had been estimated by Anderson and May (1992) are extended based on the assumptions made for the construction of the models and these are used in the study. The different phases used in the model are presented.

The model describes the behaviour of lymphoid cells in the presence of viruses. This model described three main stages. The first stage is the innate immune response stage of viral infection, the second is the overlap of innate and adaptive immune responses stage of viral infection and lastly the adaptive immune response stage which was considered by Anderson and May (1992), but with the difference that two sub-stages are considered (viremia and cell-mediated immune adaptive immune responses to viral infections). The innate immune response stage of viral infection model involves one type of lymphoid population (Natural killer cells) denoted by N and the virus population denoted by V. The overlap of innate and the adaptive immune responses stage of viral infection model also involves three types of lymphocyte populations denoted by T_c, B and N respectively. The final model which was considered by Anderson and May (1992) and which is the final stage is also considered with the inclusion of two sub-stages.

Innate immune response: Innate immune response is essential for the early detection of invading viruses which help to trigger the activation of adaptive immune responses. The rate of interaction between the virus cells (V(t)) and the natural killer cells (N(t)) occurs on the 1st day of the viral infection as they try to provide the first line of defense when the human body is infected with virus. The rate of interaction between these two cells has the following key properties:

- New lymphoid cells of (NK cells) are produced by the bone marrow at a constant rate of A_n
- NK cells die at a per capita rate of μ_n
- NK cells kill virus cells in proportion to the number of contacts between them
- The virus cells have an intrinsic growth rate when they enter a living being

Model of innate immune response: These assumptions lead to the system of differential Eq. 1 and 2:

$$N = A_n - \mu_n N + \gamma NV \tag{1}$$

$$V = rV - kVN \tag{2}$$

where, A_n corresponds to new lymphoid cell of NK cells produced. The $\mu_n N$ corresponds to the rate at which NK cells die. The γNV corresponds to the rate of growth of NK cells due to interactions with the virus cells. The term rV represents the intrinsic growth of the virus cells while kNV corresponds to the rate at which the virus cells die due to the interactions with NK cells.

Existence of steady states in the innate immune response stage: In the presence of virus cells in the human body, we considered three main stages. These were the innate immune response stage, the overlap of innate and adaptive immune responses stage and finally the adaptive immune response stage.

By system of Eq. 1 and 2, the steady states are obtained:

$$A_n - \mu_n N + \gamma NV = 0 \tag{3}$$

$$rV - pVN = 0 \tag{4}$$

where, N*, V* is a trivial steady state solution. The Jacobian matrix of system of Eq. 1 and 2 is as follows:

$$J(N,V) = \begin{bmatrix} \mu_n + \gamma V & \gamma N \\ -pV & \gamma - KN \end{bmatrix} \tag{5}$$

Overlap of innate and adaptive immune responses stage: This stage is where the T cytotoxic, T helper and B cells have just started to fight the virus cells. In this case, all the four lymphoid population types will still be in the human body before the N cells become inactive. The interaction with the virus cells has the following key properties:

- T cytotoxic cells directly kill virus cells in proportion to the number of contacts between them and they proliferate because of these contacts
- The T helper cells also activate the T cytotoxic cells to kill the virus cells
- T Helper cells do not directly interact with the virus cells, but they continue to regulate the B cells to produce antibodies to kill the virus cells and the cells proliferate as well

Model of overlap of the innate and adaptive immune responses stage: The key properties of (N, B, T_c and V) cells lead to the system of Eq. 6-9 of differential equations:

$$\frac{dN}{dt} = A_n - \mu_n N + \gamma NV \tag{6}$$

$$\frac{dB}{dt} = A_b - \mu_b B + \frac{a_b T_h B}{(1 + b_b T_h B)} + KVB \tag{7}$$

$$\frac{dT_c}{dt} = A_t - \mu_t T + \frac{a_t T_c T_h}{(1 + b_t T_c T_h)} + \rho T_c V \tag{8}$$

$$\frac{dV}{dt} = rV - KVB - \gamma VN \tag{9}$$

where, A in Eq. 6 represents the constant production rate of B, $\mu_b B$ is the self-reproduction of B cells at μ_b:

$$\mu_b = \frac{a_b T_h B}{(1 + b_b T_h B)}$$

represents the proliferation and saturation nature of the growth of the two lymphocytes ($T_h B$) as they interact. The term KVB in Eq. 7 represents growth rate of B lymphocytes as a result of the interaction with the virus cells. The term $\lambda T_c V$ in Eq. 8 represents the growth rate of T as a result of the interaction between the T cytotoxic cells and the virus cells. The term rV in Eq. 9 represents the intrinsic growth rate of the virus cells.

Existence of steady states of the overlap of innate and adaptive immune responses: By system of Eq. 6-9, we obtained steady states by putting derivatives to zero. We obtained (N*, B*, T*, V*) as a trivial steady state solution. Similarly, we obtained the Jacobian matrix as:

$$J(N,B,T_c,V) = \begin{bmatrix} -\mu_n + \gamma V & 0 & 0 & \gamma N \\ 0 & -\mu_b + \frac{a_b T_h}{(1 + b_b T_c B)^2} + KV & 0 & KB \\ 0 & 0 & -\mu_t + \frac{a_t T_h}{(1 + b_t T_c T_h)^2} & \lambda T_c \\ -\rho V & -kV & 0 & r - kB - \gamma N \end{bmatrix} \tag{10}$$

Viremia stage of adaptive immune response: B cells, T cytotoxic cells and T helper cells have been recruited to take full control in fighting the viral infection. This is because Natural killer cells are overwhelmed and have become inactive by the virus cells. Here, T helper cells activate B cells to produce more antibodies to fight the virus. The T helper cells stimulate the T cytotoxic cells to maturity to kill the virus cells directly. The interaction between the lymphocytes and the viral cells has the following key properties:

- Virus cells have an intrinsic growth rate as they are in a living being

- T helper cells activate the T cytotoxic cells to maturity to kill virus cells in proportion to the number of contacts between them and they proliferate because of these contacts
- T helper cells do not directly interact with the virus, but they continue to regulate the growth of B cells to produce more antibodies to kill the virus cells

Model of the viremia stage in the adaptive immune response stage: The rate of interaction of the cells (B, T_c, T_h and V) results in the following system of Eq. 11-14 of differential equations:

$$B' = A_b - \mu_b B + \frac{a_b T_h B}{(1 + b_b T_h B)} + KVB \tag{11}$$

$$T_c' = A_c - \mu_c T_c + \frac{a_c T_c T_h}{\left(1 + b_c T_c T_h\right)} + \lambda T_c V \tag{12}$$

$$T_h' = A_h - \mu_h T_h + \frac{a_h T_h B}{(1 + b_h T_h B)} + \rho VB \tag{13}$$

$$V' = rV - \lambda V T_c \text{ - } \rho VB \tag{14}$$

where, A_b represents the constant production rate of B, $\mu_b T_b$ is the self-reproduction of B cells at:

$$\mu_b = \frac{a_b T_h B}{(1 + b_b T_h B)}$$

represents the proliferation and saturation nature of the growth of the two lymphocytes ($T_h B$) as they interact. The term KVB in Eq. 11 represents growth rate of B lymphocytes as a result of the interaction with the virus cells. The term $\lambda T_c V$ in Eq. 12 represents the growth rate of T_c as a result of the interaction between the T cytotoxic cells and the virus cells. The term rV in Eq. 14 represents the intrinsic growth rate of the virus cells.

Existence of steady states in the viremia stage of adaptive immune response: By system of Eq. 11-14 we obtained steady states by putting derivatives to zero. We have the corresponding Jacobian matrix as:

$$J(B, T_c, T_h, V) = \begin{bmatrix} -\mu_b + \frac{a_b T_h}{\left(1 + b_b T_h B\right)^2} + KV & 0 & \frac{a_b B}{\left(1 + b_b T_h B\right)^2} & KV \\ 0 & -\mu_c + \frac{a_c T_h}{\left(1 + b_c T_c T_h\right)^2} + \lambda V & a_c T_h & \lambda T_c \\ \frac{a_h T_h}{\left(1 + b_h T_h B\right)^2} + \rho V & 0 & -\mu_h + \frac{a_h B}{\left(1 + b_h T_h B\right)^2} & \rho B \\ -\rho V & -\lambda V & 0 & r - \lambda T_c - \rho B \end{bmatrix} \tag{15}$$

Cell-mediated adaptive immune response stage: Cell-mediated immune response is very important in the fight against viral infections. This is especially with infections that involve oncogenic viruses (that is: viruses that spread directly from cell to contiguous cell). Antibody in such situations cannot reach the virus but rather virally induced antigen on the surface of the infected cell can be recognized by different effector cells such as cytotoxic T cells. Cell-mediated immune response involves T cytotoxic cells (CD^+ 8 T cells) and T helper cells (CD^+ 4 T cells).

The interaction between the lymphocytes and the viral cells has the following key properties:

- Virus cells have an intrinsic growth rate as they are in a living being
- Activated T helper cells produce a number of cytokines that defend against viruses directly
- The T cytotoxic cells have the ability of producing cytokines to directly attack the virus cells
- The interaction between T helper and T cytotoxic cells lead to proliferation and saturation of the two effector cells
- The T helper and T cytotoxic cells are the main components of cell-mediated antiviral defense

The interaction of these cells results in the following system of differential equations:

$$T_c' = A_c - \mu_c T_c + \frac{a_c T_c T_h}{\left(1 + b_c T_c T_h\right)} + \lambda T_c V \tag{16}$$

$$T_h' = A_h - \mu_h T_h + \frac{a_h T_h T_c}{\left(1 + b_h T_h T_c\right)} + \xi T_h V \tag{17}$$

$$V' = rV - \lambda V T_c T_h \tag{18}$$

where, A_c represents the constant production rate of T_c, $\mu_c T_c$ represents the self-reproduction of T cytotoxic cells at:

$$\mu_c = \frac{a_c T_c T_h}{(1 + b_c T_c T_h)}$$

represents the proliferation and saturation nature (plateau) of the growth of the two lymphocytes ($T_c T_h$) as they interact. The term $\lambda T_c V$ in Eq. 16 represents growth rate of T_c lymphocytes as a result of the interaction with the virus cells. The term rV in Eq. 18 represents the intrinsic growth rate of the virus cells. It should be noted that the dynamics of T_c and T_h cells are similar which reflects in Eq. 16-17:

Jacobian matrix of cell-mediated adaptive immune response stage:

Table 1: Parameters values supplied by Anderson and May (1992)

Lymphocytes	Initial production	Rate of increase	Rate of decrease	Death rate
T_c	$A_c = 1$	$a_c = 0.252$	$b_t = 0.008$	$\mu_t = 1.25$
T_h	$A_h = 1$	$a_h = 0.252$	$b_h = 0.008$	$\mu_t = 1.25$
B	$A_b = 1$	$a_b = 0.252$	$b_b = 0.008$	$\mu_t = 1.25$
N	$A_n = 1$	$a_n = 0.252$	$b_n = 0.008$	$\mu_n = 1.25$

$$J(T_c, T_h, V) = \begin{bmatrix} -\mu_c + \frac{a_c T_h}{(1+b_c T_h T_c)^2} + \lambda V & \frac{a_c T_h}{(1+b_c T_h T_c)^2} & \lambda T_c \\ \frac{a_h T_h}{(1+b_h T_h T_c)^2} & -\mu_h + \frac{a_h T_c}{(1+b_h T_h T_c)^2} + \xi V & \xi V \\ -\lambda V T_h & -\lambda V T_c & r - \lambda T_c T_h \end{bmatrix} \quad (19)$$

Statement of the problem: At the dawn of the 21st century humankind is faced with new, more resilient diseases including HIV/AIDS and hepatitis B that come along with a death toll from preventable infectious diseases that remain high due to poor sanitation and malnutrition among other conditions in many parts of the world. A good understanding of the dynamics of viral infections, the various stages of viral infections and the interaction of immune cells at these specific phases are important to help our natural countermeasures which could be augmented with modern medicinal techniques and immunotherapies (Table 1).

Computational procedure

MATLAB: Ordinary differential equation solver 'ode45' is used to evaluate the numerical solutions of the systems of differential equations. The MATLAB software is installed on a Laptop with the specification as Toshiba (Brand) with 4.4 rating of Windows experience index with a processor of Intel (R) Pentium (R) CPU B 960 at 2.20 GHz, memory installed is 2.00 GB and 32 bit operating system and has windows 7 ultimate edition installed. The MATLAB software version is R2009a. The data are substituted into Eq. 5, 10, 15 and 19 to get 2 by 2, 4 by 4, 4 by 4 and 3 by 3 Jacobian matrices for innate immune response stage, overlap of innate and adaptive immune responses, viremia stage of adaptive immune response and cell-mediated immune response stage respectively. MATLAB codes were written to find the equilibrium points and their corresponding eigenvalues. The eigenvalues were then classified into either a stable point or unstable point which describes the behaviour of these eigenvalues.

RESULTS

This study is an extension of the model by Anderson and May (1992) on human immune response to virus infectious diseases and it has yielded results that are in consistent with the model by these previous authors with the additional results which come along with the addition of other phases of immune response which had been captured by Anderson and May (1992). The various results of the study are presented.

Table 2: Parameters values in the model estimated by the authors

Parameters	Description	Value
r	Growth rate of virus cells	0.10
γ	Interaction rate of NK cells and V cells	0.05
λ	Interaction rate of T cytotoxic and V cells	1.20
μ_n	Death rate of NK ells	1.25
K	Death rate of virus Cells	1.25
ρ	The interaction rate of B and V cells	0.10
ξ	The interaction rate of T helper and V cells	0.85

Linearization stability analysis: Although it is usually not easy to determine the stability of an equilibrium point of a system of differential equations, the determination of the asymptotic stability is usually quite easy. The method involves linearization of the equations about the equilibrium point and the determination of the stability of the linearized equations. The numerical calculation of eigenvalues of matrices can easily be carried out with many mathematical software packages (e.g., MATLAB, MAPLE, MATHEMATICA). The linearization method examines the behaviour of the system close to equilibrium point. The stability of the equilibrium point can be determined by finding the eigenvalues of the system.

Equilibrium points in the innate immune response stage: We obtained the equilibrium points of systems of Eq. 3 and 4 by substituting the parameter values of Table 2.

$$1\text{-}1.25N+0.05\ NV = 0 \quad (20)$$

$$0.0V\text{-}1.25VN = 0 \quad (21)$$

The equilibrium points are determined by Universal Mathematics Equation Solver.

There exists two equilibrium points and these are in Eq. 22:

$$\begin{pmatrix} N^* \\ V^* \end{pmatrix} = \begin{pmatrix} 0.8 \\ 0 \end{pmatrix} \text{and} \begin{pmatrix} 0.08 \\ -225 \end{pmatrix} \quad (22)$$

Substituting the values of the parameters of Table 2 in Eq. 23, we have:

$$J\ (N,\ V)\ = \begin{bmatrix} -1.25+0.05V & 0.05N \\ -1.25V & 0.1-1.25N \end{bmatrix} \quad (23)$$

At (N*, V*) = (0.8,0) we obtained:

$$J(0.8, 0) = \begin{bmatrix} -1.25 & 0.04 \\ 0 & -0.9 \end{bmatrix} \quad (24)$$

The corresponding eigenvalues were found to be:

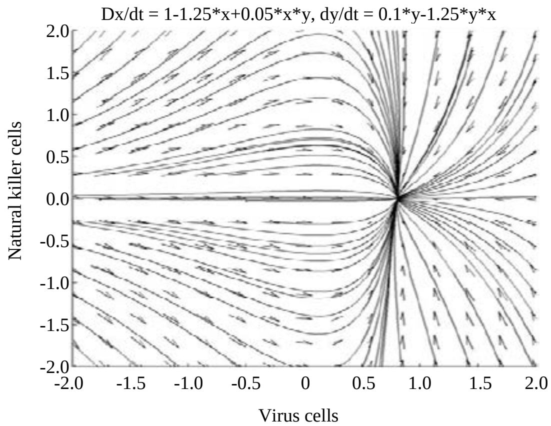

Fig. 1: Interaction between the natural killer cells and the viral cells at the early stages of viral infection

Table 3: Classification of the equilibrium points in the innate immune response stage

Equilibrium point	Eigenvalues	Classification
(0.8, 0)	λ_1 = 1.2500, λ_2 = -0.9000	Asymptotically stable
(0.08, -225)	λ_1 = -12.5894, λ_2= 0.0894	Saddle point

$$\lambda_1 = -1.2500 \text{ and } \lambda_2 = -0.9000 \tag{25}$$

At (N*, V*) = (10, -255) we obtained in Eq. 26:

$$J(10, -225) = \begin{bmatrix} -12.5 & 0.004 \\ 281.25 & 0 \end{bmatrix} \tag{26}$$

The corresponding eigenvalues are:

$$\lambda_1 = -12.5894 \text{ and } \lambda_2 = 0.0894 \tag{27}$$

It is observed from Table 3 that one of the equilibrium points is stable while the other one is unstable. This gives an assurance that even at the early stages of viral infections, the human system is somehow stable if only the natural killer cells are functioning well.

Figure 1 represents the interaction between the natural killer cells and the virus cells. The y-axis represents the N cells whiles the x-axis represents the virus cells. We observed that all the arrows converge to a particular point (0.8, 0). This confirms that there is stability when the virus cells enter the human body for the 1st week. The natural killer cells are able to suppress viral abundance to a very low level in the host within this 1st week.

Figure 2 represents the interaction between the N cells and the virus cells in the innate immune response stage. In this figure, we plot N cells and virus cells against time. The curve shows both cells decrease with time but the rate of decrease of the virus cells is greater than the rate of decrease of the N cells. The virus cells decrease drastically with time. We observed that the virus cells die faster than the natural killer cells as time increases. As a result of the interaction of the two cells, both cells decrease asymptotically as time increases. Besides, the virus cells approach a constant endemic value of about 0.001 whereas the N cells approach a fixed value of 0.8.

Equilibrium points of the overlap of innate and adaptive immune responses stage: We obtained the equilibrium points of systems Eq. 6-9 by substituting the parameter values of Table 2:

$$\frac{dN}{dt} = 1 - 1.25N + 0.05NV \tag{28}$$

$$\frac{dB}{dt} = 1 - 1.25B + \frac{0.252T_h B}{(1 + 0.008T_h B)} + 0.05VB \tag{29}$$

$$\frac{dT_c}{dt} = 1 - 1.25T + \frac{0.252T_c B}{(1 + 0.008T_c B)} + \lambda T_c V \tag{30}$$

$$\frac{dV}{dt} = 0.1V - 0.05VB - 1.25VN \tag{31}$$

MATLAB is then used to find the equilibrium points as:

$$\begin{pmatrix} N^* \\ B^* \\ T^* \\ V^* \end{pmatrix} = \begin{pmatrix} 20 \\ 0.8 \\ 20 \\ 0 \end{pmatrix} \begin{pmatrix} 1.0 \\ 0.8 \\ 1.0 \\ 0 \end{pmatrix} \begin{pmatrix} 5.0 \\ 0.8 \\ 5.0 \\ 0 \end{pmatrix} \begin{pmatrix} 0.0769 \\ 0.0769 \\ 0.0035 \\ -235 \end{pmatrix} \text{and} \begin{pmatrix} 14.2882 \pm 13.973i \\ 1.3589 \pm 0.0538i \\ 1.4416 \pm 0.6238i \\ 12.4945 \pm 5.2595i \end{pmatrix} \tag{32}$$

We realized that two of these equilibrium points involve complex numbers and therefore are neglected. By substituting parameter values, we obtained:

$$J(N, B, T, V) = \begin{bmatrix} -1.25 + 0.05V & 0 & 0 & 0.05N \\ 0 & -1.25 + \frac{0.252T_h}{(1 + 0.008T_h B)^2} + 0.05V & \frac{0.252B}{(1 + 0.008T_h B)^2} & 0.05B \\ 0 & \frac{0.05T_c}{(1 + 0.008T_c B)^2} & -1.25 + \frac{0.252B}{(1 + 0.008T_c B)^2} & 1.20V \\ -1.25V & -0.05V & 0 & 0.1 - 0.05B - 1.25N \end{bmatrix} \tag{33}$$

At (N*, B*, T*, V*) = (1, 0.8, 1, 0) we obtained:

$$J(1, 0.8, 1, 0) = \begin{bmatrix} -1.25 & 0 & 0 & 0.05 \\ 0 & -2.3019 & 0.1584 & 0.04 \\ 0 & 0.0393 & -2.3019 & 0 \\ 0 & 0 & 0 & -1.1900 \end{bmatrix} \tag{34}$$

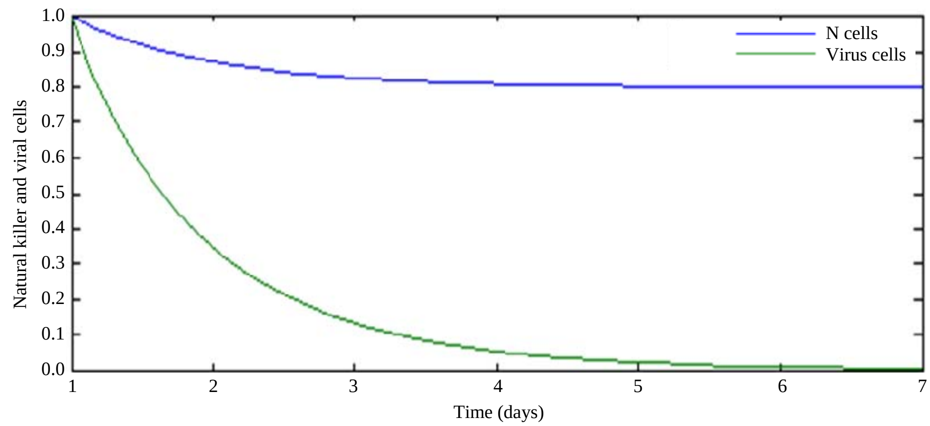

Fig. 2: Growth nature of the Natural killer cells (N) and the Viral cells (V) at the innate immune response stage

The corresponding eigenvalues were found to be:

$$\lambda_1 = -2.2230,\ \lambda_2 = -2.3808,$$
$$\lambda_3 = -1.2500 \text{ and } \lambda_4 = -1.1900 \quad (35)$$

At (N*, B*, V*) = (5, 0.8, 51, 0) we obtained:

$$J(5, 0.8, 5, 0.8) = \begin{bmatrix} -2.46 & 0 & 0 & 0.25 \\ 0 & -0.4317 & 0.12452 & 0.04 \\ 0 & 0.19648 & -2.3456 & 0.96 \\ -1 & -0.04 & 0 & -6.1900 \end{bmatrix} \quad (36)$$

The corresponding eigenvalues were found to be:

$$\lambda_1 = -6.1217,\ \lambda_2 = -2.5280,$$
$$\lambda_3 = -2.3579 \text{ and } \lambda_4 = -0.4197 \quad (37)$$

At (N*, B*, T*, V*) = (20, 0.8, 20, 0) we obtained:

$$J(20, 0.8, 20, 0) = \begin{bmatrix} -1.25 & 0 & 0 & 0.05 \\ 0 & 2.7110 & 0.1584 & 0.04 \\ 0 & 3.9611 & -1.0916 & 0 \\ 0 & 0 & 0 & -24.94 \end{bmatrix} \quad (38)$$

The corresponding eigenvalues are found to be:

$$\lambda_1 = 3.0239,\ \lambda_2 = 2.3983,$$
$$\lambda_3 = 1.2500 \text{ and } \lambda_4 = -24.9400 \quad (39)$$

At (N*, B*, T*, V*) = (0.0781, 0.07686, 0.8126, -235.1599), we obtained:

$$J(0.0769, 0.0769, 0.0035, -235) = \begin{bmatrix} -13 & 0 & 0 & 0.003845 \\ 0 & -12.9993 & 0.01523 & 0.003845 \\ 0 & 0.00013 & -1.2348 & -282 \\ 293.75 & -11.758 & 0 & -0.00003 \end{bmatrix} \quad (40)$$

The corresponding eigenvalues are found to be:

$$\lambda_1 = 1.4035,\ \lambda_2 = 2.8973,$$
$$\lambda_3 = 12.740 \text{ and } \lambda_4 = -13.0002 \quad (41)$$

It is observed from Table 4 that there is greater percentage of stability when (NK, T_c and B cells) get recruited to fight the infection. The behaviour of two of the equilibrium points are asymptotically stable while the other two are not stable.

Figure 3 represents the overlap of innate and adaptive immune response stage of viral infection. In this figure, we plot N cells, T cytotoxic cells, B cells and virus cells against time. We observed that B and T cells increase to a certain peak value of 20 and approach this constant endemic value as time increases. However, the N killer cells and the virus cells decrease to certain constants values of about 0.8 and 0.0001, respectively. This confirms the fact that the N cells get overwhelmed and become inactive after some time of viral infection.

Equilibrium points in the viremia stage of adaptive immune response: We obtained the equilibrium points of Eq. 11-14 by substituting the parameter values of Table 2.

$$1 - 1.25B + \frac{0.252T_hB}{(1 + 0.008T_hB)} + 1.25VB = 0 \quad (42)$$

$$1 - 1.25T_c + \frac{0.252T_cT_h}{(1 + 0.008T_cT_h)} + 1.20T_cV = 0 \quad (43)$$

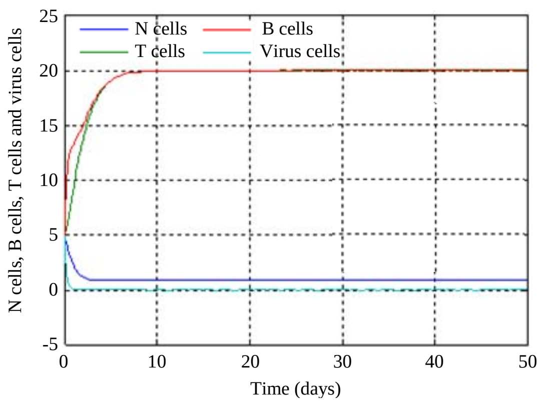

Fig. 3: Growth nature of the viral cells and the immune cells (Natural killer cells, T cells and B lymphocytes) at the overlap of innate and adaptive immune responses stage

$$1-1.25T_h+\frac{0.252T_hB}{(1+0.008T_hB)}+0.1VB=0 \quad (44)$$

$$0.1V-1.20VT_c\text{ -}1.25VB=0 \quad (45)$$

MATLAB is then used to find the equilibrium points as:

$$\begin{pmatrix} B^* \\ T_c^* \\ T_h^* \\ V^* \end{pmatrix}=\begin{pmatrix} -10.0792 \\ 35.5400 \\ -0.0735 \\ 4.9196 \end{pmatrix},\begin{pmatrix} -1.4616 \\ 0.4864 \\ -1.6365 \\ 1.4487 \end{pmatrix},\begin{pmatrix} 0.0810 \\ 0.7538 \\ 0.0841 \\ -9.0231 \end{pmatrix},\begin{pmatrix} 0.5379 \\ 0.8650 \\ 0.5479 \\ -0.6609 \end{pmatrix} \quad (46)$$

And four other complex equilibrium points which have been displayed in the Appendix.

We evaluated the equilibrium points by substituting the parameter values of Table 3-4:

$$J(B,T_c,T_h,V)=\begin{bmatrix} -1.25+\frac{0.252T_h}{(1+0.008T_hB)^2}+1.25V & 0 & \frac{0.252B}{(1+0.008T_hB)^2} & 1.25V \\ 0 & -1.25+0.252T_h+1.20V & 0.252T_c & 1.25T_c \\ \frac{0.252T_h}{(1+0.008T_hB)^2}+0.10V & 0 & -1.25+\frac{0.252B}{(1+0.008T_hB)^2} & 0.10B \\ -0.10V & 1.20V & 0 & 0.10-1.20T_c-0.10B \end{bmatrix} \quad (47)$$

At (B^*, T_c^*, T_h^*, V^*) = (-10.0792, 35.5400, -0.0735, 4.9196) we obtained:

$$J(-10.0792,35.5400,-0.0735,4.9196)=\begin{bmatrix} 13.7503 & 0 & -2.5101 & 6.1495 \\ 0 & 4.635 & 8.9561 & 44.425 \\ 0.4737 & 0 & -3.7601 & -0.1008 \\ -0.4920 & 5.9035 & 0 & -41.5401 \end{bmatrix} \quad (48)$$

The corresponding eigenvalues were found as:

$$\lambda_1=-46.6113,\ \lambda_2=-3.6669,\ \lambda_3=13.6031\text{ and }\lambda_4=9.7602 \quad (49)$$

At (B^*, T_c^*, Th^*, V^*) = (-1.4616, 0.4864, -1.6365, 1.4487), we obtained:

$$J(-1.4616,0.4864,-106365,1.4487)=\begin{bmatrix} 0.1451 & 0 & -0.3640 & 1.8109 \\ 0 & 0.0760 & 0.1226 & 0.6080 \\ -0.2627 & 0 & -1.6140 & -0.1462 \\ -0.1449 & 1.7304 & 0 & -0.3375 \end{bmatrix} \quad (50)$$

The eigenvalues were found as:

$$\lambda_1=0.6865,\ \lambda_2=0.3353,\ \lambda_3=-1.6458\text{ and }\lambda_4=-1.10064 \quad (51)$$

At (B^*, T_c^*, T_h^*, V^*) = (0.0810, 0.7538, 0.0841, -9.0231), we obtained:

$$J(0.0810,0.7538,0.0841,-9.0231)=\begin{bmatrix} -12.5079 & 0 & 0.0202 & -11.2789 \\ 0 & -12.0565 & 0.1900 & 0.9423 \\ -0.8814 & 0 & -1.2980 & -0.9024 \\ 0.9023 & -10.8277 & 0 & -0.8127 \end{bmatrix} \quad (52)$$

The corresponding eigenvalues were found as:

$$\lambda_1=-12.2183,\ \lambda_2=-10.1715,\ \lambda_3=-2.9879\text{ and }\lambda_4=-1.2974 \quad (53)$$

At (B^*, T_c^*, T_h^*, V^*) = (0.5379, 0.8650, 0.5479, -0.6609), we obtained:

$$J(0.5379,0.8650,0.5479,-0.6609)=\begin{bmatrix} -3.1897 & 0 & 0.1340 & -0.8261 \\ 0 & -109050 & 0.0218 & 1.0813 \\ 0.07036 & 0 & -1.1160 & 0.0538 \\ 0.0661 & -0.7931 & 0 & -0.9918 \end{bmatrix} \quad (54)$$

The corresponding eigenvalues were as below:

$$\lambda_1=-3.1767,\ \lambda_2=-1.4653+0.8241i,\ \lambda_3=-1.4653-0.824i\text{ and }\lambda_4=-1.0953 \quad (55)$$

Table 5 displays the classification of equilibrium points of the viremia stage of adaptive immune response. Two of the equilibrium points are unstable while the other two equilibrium points are stable.

Figure 4 presents the viremia stage of adaptive immune response which involves the interaction between B cells, T cytotoxic cells, T helper cells and the virus cells. In this figure, we plot B cells, T cytotoxic cells, T helper cells and

Table 4: Classification of the equilibrium points in the overlap of innate and adaptive immune responses

Equilibrium point	Eigenvalues	Classification
(1, 0.8, 1, 0)	λ_1 = -2.2230, λ_2 = -2.3808, λ_3 = -1.2500 and λ_4 = -1.1900	Asymptotically stable
(5, 0.8, 5, 0.8)	λ_1 = -6.1217, λ_2 = -2.5280, λ_3 = -2.3579 and λ_4 = -0.4197	Asymptotically stable
(20, 0.8, 20, 0)	λ_1 = 3.0239, λ_2 = 2.3983, λ_3 = -1.250 and λ_4 = -24.94	Saddle point
(0.0769, 0.0769, 0.0035, -235)	λ_1 = 1.4035, λ_2 = -2.8973, λ_3 = -12.740 and λ_4 = -13.00	Saddle point

Table 5: Classification of the equilibrium points in the viremia stage of immune response

Equilibrium point	Eigenvalues	Classification
(-10.0792, 35.54, -0.0735, 49196)	λ_1 = -46.6113, λ_2 = -3.6669, λ_3 = 13.6031, λ_4 = 9.7602	Unstable point
(-1.4616, 0.4864, -1.6365, 1.4487)	λ_1 = 0.6865, λ_2 = 0.3353, λ_3 = -1.6458, λ_4 = -1.1064	Unstable point
(0.081, 0.7538, 0.0841, -9.023)	λ_1 = -12.218, λ_2 = -10.172, λ_3 = -2.988, λ_4 = -1.297	Asymptotically stable
(0.538, 0.865, 0.548, -0.661)	λ_1 = -3.177, λ_2 = -1.465+0.824i, λ_3 = -1.465-0.824i, λ_4 = -1.095	Stable sink

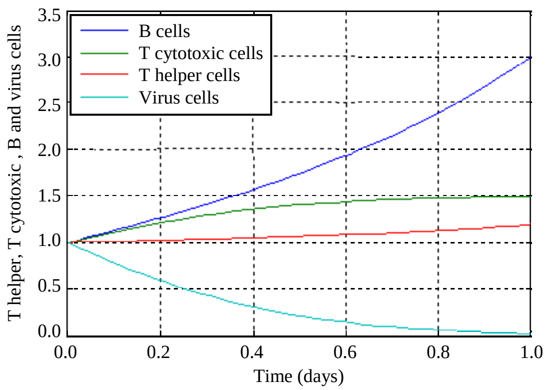

Fig. 4: Growth nature of the viral cells V and the immune cells (T helper, T cytotoxic and B lymphocytes) at the viremia stage of adaptive immune response

virus cells against time in days. We observe that B cells, T cytotoxic cells and T helper cells rise to peak values of 3.0, 1.5 and 1.2, respectively. There is a very sharp increase in B as compared with T cytotoxic and T helper cells. On the other hand, virus cells decrease drastically towards zero. This indicates that B cells are more active in the viremia stage of immune response to viral infections.

Cell-mediated stage of adaptive immune response: By substituting parameter values into Eq. 16-18, we obtained the Jacobian matrix hence finding the corresponding equilibrium points using MATLAB:

$$J(T_c, T_h, V) = \begin{bmatrix} -\mu_c + \dfrac{a_c T_h}{(1+b_c T_c T_h)^2} + \lambda V & \dfrac{a_c T_h}{(1+b_c T_h T_c)^2} & \lambda T_c \\ \dfrac{a_h T_h}{(1+b_c T_h T_c)^2} & -\mu_h + \dfrac{a_h T_c}{(1+b_h T_h T_c)} + \xi V & \xi T_h \\ -\lambda V T_h & -\lambda V T_c & r - \lambda T_c T_h \end{bmatrix} \quad (56)$$

The equilibrium points are as follows:

$$\begin{pmatrix} T_c^* \\ T_h^* \\ V^* \end{pmatrix} = \begin{pmatrix} 1 \\ 1 \\ 0 \end{pmatrix}, \begin{pmatrix} 5 \\ 5 \\ 0 \end{pmatrix}, \begin{pmatrix} 20 \\ 20 \\ 0 \end{pmatrix}, \begin{pmatrix} 0.3221 \\ 0.2583 \\ -2.252 \end{pmatrix}, \begin{pmatrix} -0.3646 \\ -0.2285 \\ 4.7646 \end{pmatrix} \quad (57)$$

We evaluate the equilibrium points by substituting the parameter values of Table 2 into Eq. 19:

$$J(T_c, T_h, V) = \begin{bmatrix} -1.25 + \dfrac{0.252 T_c}{(1+0.008 T_c T_h)^2} + 1.20V & \dfrac{0.252 T_h}{(1+0.008 T_h T_c)^2} & 1.20 T_c \\ \dfrac{0.252 T_h}{(1+0.008 T_h T_c)^2} & -1.25 + \dfrac{0.252 T_c}{(1+0.008 T_h T_c)^2} + 0.85V & 0.85 T_h \\ -1.20 V T_h & -1.20 V T_c & 0.1 - 1.20 T_h T_c \end{bmatrix} \quad (58)$$

At (B^*, T_c^*, T_h^*, V^*) = (1, 1, 0) we obtained:

$$J(1,1,0) = \begin{bmatrix} -2.253 & 0.248 & 1.20 \\ 0.248 & -2.253 & 0.85 \\ 0 & 0 & -1.1 \end{bmatrix} \quad (59)$$

The corresponding eigenvalues were found to be:
λ_1 = -2.0050, λ_2 = -2.5010 and λ_3 = -1.100

At (B^*, T_c^*, T_h^*, V^*) = (5, 5, 0), we obtained:

$$J(5,5,0) = \begin{bmatrix} -1.892 & 0.6076 & 6 \\ 0.6076 & -1.892 & 4.25 \\ 0 & 0 & -29.9 \end{bmatrix} \quad (60)$$

The corresponding eigenvalues were found to be:

λ_1 = -1.2844, λ_2 = -2.4996 and λ_3 = -29.90

At (B^*, T_c^*, T_h^*, V^*) = (0.3221, 0.2583, -2.252), we obtained:

$$J(20,20,0) = \begin{bmatrix} -2.3136 & 0.1864 & 24 \\ 0.1864 & -2.3136 & 17 \\ 0 & 0 & -479.9 \end{bmatrix} \quad (61)$$

The corresponding eigenvalues were found to be:

λ_1 = -2.1272, λ_2 = -2.50 and λ_3 = -479.90

At (B^*, T_c^*, T_h^*, V^*) = (0.3221, 0.2583, -2.252), we obtained:

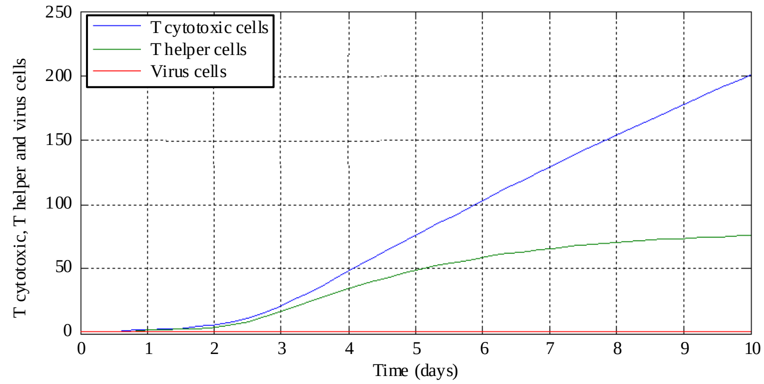

Fig. 5: Growth nature of the viral cells V and the immune cells (T cytotoxic and T helper cells)

Table 6: Classification of the equilibrium points in the cell-mediated stage of adaptive immune response

Equilibrium points	Eigenvalues	Classification
(1, 1, 0)	λ_1 = -2.0050, λ_2 = -2.5010 and λ_3 = -1.100	Asymptotically stable
(5, 5, 0)	λ_1 = -1.2844, λ_2 = -2.4996 and λ_3 = -29.90	Asymptotically stable
(20, 20, 0)	λ_1 = -2.1272, λ_2 = -2.50 and λ_3 = -479.90	Asymptotically stable
(0.3221, 0.2583, -2.252)	λ_1 = 0.1296, λ_2 = -3.9391 and λ_3 = -3.1447	Saddle point
(-0.3646, -0.2285, 4.7646)	λ_1 = 0.1296, λ_2 = -3.9391 and λ_3 = -3.1447	Saddle point

$$J\left(T_c^*, T_h^*, V^*\right) = \begin{bmatrix} -3.8713 & 0.065 & 0.3865 \\ 0.065 & -3.083 & 0.2196 \\ 0.698 & 0.8704 & 0.00016 \end{bmatrix} \quad (62)$$

The eigenvalues were found to be:

$$\lambda_1 = 0.1296,\ \lambda_2 = -3.9391 \text{ and } \lambda_3 = -3.1447$$

At (B^*, T_c^*, T_h^*, V^*) = (-0.3646, -0.2285, 4.7646), we obtained:

$$J\left(T_c^*, T_h^*, V^*\right) = \begin{bmatrix} 4.376 & -0.0575 & -0.4375 \\ -0.0575 & 2.7082 & -0.1942 \\ 1.3065 & 2.0846 & 0.00003 \end{bmatrix} \quad (63)$$

The eigenvalues were found to be:

$$\lambda_1 = 0.1296,\ \lambda_2 = -3.9391 \text{ and } \lambda_3 = -3.1447$$

Table 6 displayed the equilibrium points in the cell mediated stage of the adaptive immune response. This is the last stage of immune cells' destruction of viral infections. The behavior of the equilibrium points show stability more than the other stages provided there are no deficiencies with the two main cells (T_h and T_c) that are the main components of the last phase of viral destruction.

Figure 5 the cell-mediated stage of adaptive immune response stage of viral infection. This involves the interaction between T cytotoxic cells and T helper cells, respectively (CD^+ 8 cells and CD^+ 4 cells). We plot T cytotoxic, T helper and Virus cells against time in days. We observed that virus cells approaches zero with time. There is a sharp increase in the growth of T helper and T cytotoxic cells as time increases. The growth rate of T cytotoxic cells is very fast as compared to T helper cells. We observed that as T cytotoxic approaches a certain endemic value of 200, T helper cells approach a constant endemic value of 70 within the same duration of growth. We observe that at this last phase of immune response to viral infections, the viral load approaches zero. This shows that T cytotoxic cells are more active than the T helper cells.

RESULTS

This study is an extension of Anderson and May (1992) model on human immune response to virus infectious diseases and it has yielded results that are in consistent with these workers except that this current study included the dynamics of a third lymphoid cell (Natural Killer Cells) which provide a first line of defence and if a therapy is designed for it, viral infections could be compacted faster. In the presence of viruses Anderson and May (1992) considered only one phase of the adaptive immune response and had three different behaviour of the equilibrium states which are two unstable states at:

$$\lambda_1 = -1.25,\ \lambda_2 = -0.75397 \text{ and } \lambda_3 = 0.09 \text{ and}$$
$$\lambda_1 = -1.25\ \lambda_2 = 0.05 \text{ and } \lambda_3 = 0.05$$

respectively and one asymptotically equilibrium state as λ_1 = -1.25, λ_2 = -0.6785 and λ_3 = -0.1. The last stage of immune response which was considered by Anderson and May (1992), which yielded three steady states gives five behaviour of steady states in this current study and these are three asymptotically stable states and two unstable states.

The current study realizes two behaviour of equilibrium points at the innate immune response stage (the first line of defense) that was not considered by Anderson and May (1992) and these are.

$\lambda_1 = -1.25$ and $\lambda_2 = -0.90$-asymptotically stable and $\lambda_1 = -12.5894$ and $\lambda_2 = 0.0894$-saddle point. Four behaviour of equilibrium points are realized at the overlap stage of immune response and these are: $\lambda_1 = -2.2230$ $\lambda_2 = -2.3808$, $\lambda_3 = -1.2500$ and $\lambda_4 = -1.1900$-asymptotically stable: $\lambda_1 = -6.1217$, $\lambda_2 = -2.5280$, $\lambda_3 = -2.3579$ and $\lambda_4 = -0.4197$: $\lambda_1 = -3.0239$, $\lambda_2 = -2.3983$, $\lambda_3 = -1.250$ and $\lambda_4 = -24.94$-asymptotically stable: $\lambda_1 = -1.4035$ $\lambda_2 = -2.8973$, $\lambda_3 = -12.740$ and $\lambda_4 = -13.00$-saddle point and finally-saddle point. These behaviour indicate the systematic stability that the human system maintains at the various stages of immune response to viral infections. The viremia stage gives only one stable state of equilibrium since NK cells become inactive and T helper cells are also not active. The only stable state is:

$$\lambda_1 = -3.177 \quad \lambda_2 = -1.465+0.824i,$$
$$\lambda_3 = -1.465-0.824i \text{ and } \lambda_4 = -1.095$$

which is also a stable sink. All the rest of the equilibrium points give unstable states and these are:

$$\lambda_1 = -46.6113, \quad \lambda_2 = -3.6669,$$
$$\lambda_3 = 13.6031 \text{ and } \lambda_4 = 9.7602$$

$$\lambda_1 = 0.6865, \quad \lambda_2 = 0.3353,$$
$$\lambda_3 = 1.6458 \text{ and } \lambda_4 = -1.1064$$

$$\lambda_1 = -12.218, \quad \lambda_2 = -10.172,$$
$$\lambda_3 = -2.988 \text{ and } \lambda_4 = -1.287$$

The study also considered the dynamics of the two types of T cells thus T cytotoxic and T helper cells that have different dynamics. The inclusion of these cells have helped to explain the viral infection in a wider perspective. We realized that there is stability in the human body when the virus cells enter the body. All the models considered give an equilibrium state that is asymptotically stable. At this point, the lymphoid cells are said to be in the immune state and any further infections result in a rapid re-equilibration. The models, therefore, display all of the major macroscopic characteristics of the human immune response to viral infections.

DISCUSSION

This results is in consistent with the results of Anderson and May (1992) which predicts two different types of study states thus a stable state and an unstable state even though their model is on two lymphocyte population types and this current study also considers four lymphocyte types. The unique aspect of this study is the inclusion of other two types of effector cells thus Natural Killer cells and T helper cells (NK cells and CD^+ 4 cells). The current study had considered the immune response to viral infection in a wider perspective and each of the models at the specific stages of immune response also predicts two different types of steady states thus a stable state and an unstable state. The model of Bittner and Wahl (2000) predicts the existence of four different types of study states thus a state of no infection, infection being controlled by immune cells, all mutants held in check by T lymphocytes and responses to both conserved and variable epitopes control the infection. The results of Bittner and Wahl (2000) are in consistent with the results of both the current study and the study of Anderson and May (1992). The main immune cell studied in the model of Wodarz (2004) is cytotoxic T lymphocytes and the results show that T lymphocytes induce pathology in the clearance of viral cells and also suppress viremia to a certain degree but there is no obvious correlation between pathology and viral load. The study of this author is on Hepatitis C Virus infection. The results of this current study is in consistent with the results of Wodarz (2004), since the numerical simulation analysis shows the suppression of the viral load at all the stages of viral clearance. The simulation and sensitivity analysis of the model of Hancioglu *et al*. (2007) shows that the diseases fall into either of these three categories: asymptomatic diseases, typical diseases and severe diseases which represent various viral loads and the analysis of the adaptive immune response showed that whenever there is sufficient antibody response with enough specificity, the health of the host will restore, irrespective of the intensity of the innate response. The results of Hancioglu *et al*. (2007) are in consistent with this current study since the simulation analysis of the final stage of the adaptive immune response of the current study showed enough stability in the host. The categories with their corresponding viral loads also corresponds to the continuous reduction of viral load at the various stages of this current study. The results of the study of Wiah *et al*. (2011) showed the existence of disease free and endemic equilibrium states. The analysis of the adaptive immune response stage of this same study showed that with sufficient antibody response with enough specificity, the dynamics is able to restore the health of the host irrespective of the intensity of the innate response. The results of Nakata (2011) showed three possible equilibria and these are an uninfected equilibrium and infected equilibrium with or without immune response depending on the basic reproduction number for viral infections. This results is also in consistent with the results of the current study which are infection equilibrium (unstable state) and infection free equilibrium (asymptotically stable equilibrium state). The model of Tian and Wang (2015), established two threshold parameters which represents the infection-free equilibrium and the endemic equilibrium respectively. This results is also in the consistent with the results of the current study.

This study has extended the work of Anderson and May (1992) which considered only the adaptive immune response stage of viral infection and also dealt with two main effector cells thus (T cytotoxic and B cells) to four main stages with four main effector cells thus (T_c, T_h, B and NK cells) thus innate, overlap of innate, viremia and cell-mediated immune responses stage. The system of three differential equations by Anderson and May (1992) of the adaptive immune response stage has been extended to a system of four differential equations yielding three asymptotical stabilities as compared to the one asymptotical stability in the adaptive immune response stage in the work of Anderson and May (1992). By numerical simulation analysis, the immune system is seen to be very effective in the fight of viral infections if the specific immune cells (T_c, T_h, B and NK cells) function effectively. By stability analysis, there is the state of infection free steady state(s) at each stage of the stages of immune response to viruses that corresponds to the asymptotical stability which represents the ability of the immune cells (T_c, T_h, B and NK cells) to fight viruses without the activation by drugs if there are no deformities of these cells. In summary, all the equilibrium points fall into either an asymptotical stable state or unstable state as compared to the study of Bittner and Wahl (2000) which shows four main stability states. The state of endemic steady state where the equilibrium points are unstable represents the immune-deficiency as a results of one or more of these cells not functioning properly or such cells may be absent altogether. The simulation analysis shows that at all the stages of immune response to viral infections, the cells of the immune system considered increase as viral load decreases which agrees with the three categories of viral loads of the study of Hancioglu *et al*. (2007). In summary, the stability analysis in the current study is in consistent with the results of Anderson and May (1992), Bittner and Wahl (2000), Wodarz (2004), Hancioglu *et al*. (2007), Wiah *et al*. (2011), Nakata (2011) and Tian and Wang (2015).

CONCLUSION

It can be concluded that the characteristics and growth nature of the immune cells are different thus it is recommended that further research be carried out on variable sensitivity analysis and also bifurcation analysis to determine the specific immune cell which is paramount to fight viral infection and at what specific stage it will function. It is also recommended that further research be carried on a specific viral infection in the near future which could predict an immunotherapy for such a viral infection.

Appendix: MATLAB Codes for numerical solutions and simulations

```
3/22/15 1:47 PM                 MATLAB Command Window                              1 of 1

>> eqs4='1-1.25*n+0.05*n*v,1-1.25*b+(0.252*t*b)/(1+0.008*t*b)+0.05*v*b,1-1.25*t+0.252*t*b/↙
(1+0.008*t*b)+1.20*t*v,0.1*v-0.05*v*b-1.25*v*n';
[n,b,t,v]=solve (eqs4)

n =
                                                                       20.0
                                                                        1.0
                                                                        5.0
                                             0.076928139428920685852566582650375
   14.288195152954606332500831944626*i - 31.973246678410112516839326769586
 - 14.288195152954606332500831944626*i - 31.973246678410112516839326769586

b =
                                                                        0.8
                                                                        0.8
                                                                        0.8
                                             0.076922874422843172565897336693985
  1.3589298671364045006735730707834 - 0.57152780611818425330003327778503*i
  0.57152780611818425330003327778503*i + 1.3589298671364045006735730707834

t =
                                                                       20.0
                                                                        1.0
                                                                        5.0
                                            0.0035306815370105384220461927991408
   0.62375851277973591704806890677152*i + 1.4416131753431043237084057886 37
   1.4416131753431043237084057886 37 - 0.62375851277973591704806890677152*i
v =
                                                                          0
                                                                          0
                                                                          0
                                              -235.00068445259190025532928481318
   12.494516660383832950567438678226 - 5.2594557161358781260533913617437*i
   5.2594557161358781260533913617437*i + 12.494516660383832950567438678226

  >> ++31
```

```
3/22/15 8:45 PM                MATLAB Command Window                1 of 1

>> J=[-1.25,0,0,1;0,2.7111,0.1245,0.004;0,0.7859,2.7111,0;0,0,0,-24.94];
lambda=eig(J)

lambda =

    3.0239
    2.3983
   -1.2500
  -24.9400

>> K=[-1.25,0,0,0.05;0,-2.3019,0.15844,0.05;0,0.0393,-2.3019,0.04;0,0,0,-1.1900];
lambda=eig(K)

lambda =

   -2.2230
   -2.3808
   -1.2500
   -1.1900

>> L=[-2.46,0,0,0.25;0,-0.4317,0.1245,0.04;0,0.19648,-2.3456,0.96;-1,-0.04,0,-6.19];
lambda=eig(L)

lambda =

   -6.1217
   -2.5280
   -2.3579
   -0.4197

>> M=[-13,0,0,0.00385;0,-12.9993,0.01523,0.00385;0,0.000138,-1.2348,-282;293.75,↙
-11.75,0,0.00003];
lambda=eig(M)

lambda =

    1.4035
   -2.8973
  -12.7400
  -13.0002

>>
```

```
3/23/15 10:27 PM                MATLAB Command Window                1 of 1

>> eqs9='1-1.25*b+0.252*b*h/(1+0.008*b*h)+1.25*v*b,1-1.25*t+0.252*t*h+1.20*t*v,1-1.25*h+0.↙
252*b*h/(1+0.008*b*h)+0.1*v*b,0.1*v-1.20*t*v-1.25*t*b';
[b,t,h,v]=solve (eqs9)

b =

                                    -10.07921130264838794982203814072
                                   -1.4615901379635867701207132146362
                                  0.081044021553026695234089752733822
                                   0.53794812954584123197605050424836
 2.3543842536103182780996377979055*i + 2.4163693505738574204552053137759
   3.39794593124414267588139026356*i + 1.8234101735485213134494405174067
   1.8234101735485213134494405174067 - 3.39794593124414267588139026356*i
 2.4163693505738574204552053137759 - 2.3543842536103182780996377979055*i
```

```
3/29/15 9:15 PM                MATLAB Command Window                1 of 1

>>  eqs91='1-1.25*b+0.252*b*h/(1+0.008*b*h)+1.25*v*b,1-1.25*t+0.252*t*h+1.20*t*v,1-1.25↙
*h+0.252*b*h/(1+0.008*b*h)+1.25*v*b,1.28*v-1.20*t*v-1.25*t*b';
[b,t,h,v]=solve(eqs91)

b =

                                        -2.308303819031577402205050154763 7
 0.5211320981619308397678165170122 8 - 0.3605982018134812270837109287434 5*i
```


```
3/29/15 9:15 PM                MATLAB Command Window                1 of 1

>>  eqs91='1-1.25*b+0.252*b*h/(1+0.008*b*h)+1.25*v*b,1-1.25*t+0.252*t*h+1.20*t*v,1-1.25↙
*h+0.252*b*h/(1+0.008*b*h)+1.25*v*b,1.28*v-1.20*t*v-1.25*t*b';
[b,t,h,v]=solve(eqs91)

b =

                                        -2.3083038190315774022050501547637
 0.52113209816193083976781651701228 - 0.36059820181348122708371092874345*i
   12.430080857882859323483990406856*i + 4.0031434148379331786467788277081
   7.787868762664375751580377148889 6*i - 1.0647870821430771995931914964172
 0.36059820181348122708371092874345*i + 0.52113209816193083976781651701228
 - 7.7878687626643757515803771488896*i - 1.0647870821430771995931914964172
   4.0031434148379331786467788277081 - 12.430080857882859323483990406856*i


t =

                                        -2.3083038190315774022050501547637
 0.52113209816193083976781651701228 - 0.36059820181348122708371092874345*i
   12.430080857882859323483990406856*i + 4.0031434148379331786467788277081
   7.7878687626643757515803771488896*i - 1.0647870821430771995931914964172
 0.36059820181348122708371092874345*i + 0.52113209816193083976781651701228
 - 7.7878687626643757515803771488896*i - 1.0647870821430771995931914964172
   4.0031434148379331786467788277081 - 12.430080857882859323483990406856*i
```

```
3/29/15 9:15 PM                    MATLAB Command Window                    1 of 1
h =

                                           -3.1270348387713496780007840927685
   0.53425072072661073343673747186798 - 0.35852678865982699560009542903909*i
  0.15896567407997017732532116384176*i + 0.084714797562780693158198281778671
 - 0.48661765431350562780509315464832*i - 0.41942429438416498549612419158832
   0.35852678865982699560009542903909*i + 0.53425072072661073343673747186798
   0.48661765431350562780509315464832*i - 0.41942429438416498549612419158832
  0.084714797562780693158198281778671 - 0.15896567407997017732532116384176*i

v =

                                           1.79290360874636786726022166275
  - 0.6460071666595659845573836154889*i - 0.14324513868370154728400378451535
      1.472423843119628251889908729404*i - 1.9747371406943394603137309927268
     2.1121554750048570739676239458672 - 2.6180099076847806425949520818652*i
    0.6460071666595659845573836154889*i - 0.14324513868370154728400378451535
     2.6180099076847806425949520818652*i + 2.1121554750048570739676239458672
    - 1.472423843119628251889908729404*i - 1.9747371406943394603137309927268

 >>
```

```
3/29/15 9:46 PM                    MATLAB Command Window                    1 of 2

>> eqs101='1-1.25*b+0.252*b*h/(1+0.008*b*h)+1.25*v*b,1-1.25*t+0.252*t*h/(1+0.008*h*t)+1.↙
20*t*v,1-1.25*h+0.252*b*h/(1+0.008*b*h)+1.25*v*b,0.1*v-1.20*t*v-1.25*t*b';
[b,t,h,v]=solve(eqs101)

b =

                                          0.54784513812813845239656514912214
                                          -1.7941279520849137442243435308909
                                         0.081104003219724948762279984164653
                                           -1.727403914301265731296114697988
                                          0.52002134117481596142134455284746
   11.500908398471245954316373110644*i + 0.82270878622884985332619496782394
   9.6655124037352359077577765839018*i - 0.44082698816381754004745731567301
   10.063953438633371557578096698089*i + 0.12103024182910018833246244994239
   0.12103024182910018833246244994239 - 10.063953438633371557578096698089*i
 - 9.6655124037352359077577765839018*i - 0.44082698816381754004745731567301
   0.82270878622884985332619496782394 - 11.500908398471245954316373110644*i

t =

                                          0.54784513812813845239656514912214
                                          -1.7941279520849137442243435308909
                                         0.081104003219724948762279984164653
                                           -1.727403914301265731296114697988
                                          0.52002134117481596142134455284746
   11.500908398471245954316373110644*i + 0.82270878622884985332619496782394
   9.6655124037352359077577765839018*i - 0.44082698816381754004745731567301
   10.063953438633371557578096698089*i + 0.12103024182910018833246244994239
   0.12103024182910018833246244994239 - 10.063953438633371557578096698089*i
 - 9.6655124037352359077577765839018*i - 0.44082698816381754004745731567301
   0.82270878622884985332619496782394 - 11.500908398471245954316373110644*i
  h =

                                             -211.9233251014393976934246298151
                                             -2.129883682855496386851970026044
                                           0.08413375200089976065603304479999
                                              38.839612429698708816170902861674
                                            0.52886201487173342634333001835544
   0.028399386006264018812185674618466*i + 0.045506386501574159479995657506582
  - 0.14204123915928157804988406438495*i - 0.060150162150111823217265684846002
      9.9689759813867883004712981676927*i + 0.14143360252158584399736130111922
      0.14143360252158584399736130111922 - 9.9689759813867883004712981676927*i
    0.14204123915928157804988406438495*i - 0.060150162150111823217265684846002
   0.045506386501574159479995657506582 - 0.028399386006264018812185674618466*i


  v =

                                        -0.57044770516651826152670814327312
```

3/29/15 9:50 PM MATLAB Command Window 2 of 2

```
                                                 1.7985150039086140508287631053964
                                                -8.8802277921143639749426807989198
                                                 1.8032480828833834533774592919951
                                                -0.64300839295477163100340582792418
      5.8049794997426390362212066646393*i - 12.32156708410099651694473487461
      3.248102837116103777227961503668 - 6.9816137888618753796939512142806*i
  - 10.482741703198782393916030874717*i - 0.21370891239173657175217550371023
    10.482741703198782393916030874717*i - 0.21370891239173657175217550371023
      6.9816137888618753796939512142806*i + 3.248102837116103777227961503668
    - 5.8049794997426390362212066646393*i - 12.32156708410099651694473487461
```

4/25/15 6:24 PM MATLAB Command Window 1 of 1

```
>> eqs17='1-1.25*t+0.252*t*h/(1+0.008*t*h)+1.20*t*v,1-1.25*h+0.252*t*h/(1+0.008*t*h)+0.
85*h*v,0.1*v-1.20*t*h*v';
[t,h,v]=solve(eqs17)

t =

                              1.0
                              5.0
                             20.0
  0.32263449119674238891245452669129
 -0.36464501481891556487125566541758


h =

                              1.0
                              5.0
                             20.0
  0.25829021883006519178380609633745
 -0.22853276459769252547965528973967


v =

                              0
                              0
                              0
 -2.2523863497157964313235835808644
  4.7646412516765807450490737769428

>>
```

4/5/15 1:58 PM C:\Users\MADAM HAWA ADUSEI\Documents\MATLAB\ydm.m 1 of 1

```
function ydm=ydm(t,y)
ydm=[1-1.25*y(1)+0.05*y(1)*y(2);0.1*y(2)-1.25*y(1)*y(2)];

function overlap2 =overlap2(t,y)
overlap2(1)=1-1.25*y(1)+0.05*y(1)*y(4);
overlap2(2)=1-1.25*y(2)+0.252*y(3)*y(2)/(1+0.008*y(3)*y(2))+0.05*y(4)*y(2);
overlap2(3) =1-1.25*y(3)+0.252*y(2)*y(3)/(1+0.008*y(2)*y(3))+1.20*y(3)*y(4);
overlap2(4) =0.1*y(4)-0.05*y(4)*y(2)-1.25*y(4)*y(1);
overlap2 = [overlap2(1) overlap2(2) overlap2(3) overlap2(4)]';

function adaptive =adaptive(t,y)
adaptive(1)=1-1.25*y(1)+0.252*y(3)*y(1)/(1+0.008*y(3))*y(1)+1.25*y(1);
adaptive(2) =1-1.25*y(3)+0.252*y(2)*y(3)+1.20*y(2)*y(4);
adaptive(3) =1-1.25*y(3)+0.252*y(3)*y(1)/(1+0.008*y(3)*y(1))+0.1*y(4)*y(1);
adaptive(4)=0.1*y(4)-1.20*y(4)*y(2)-1.25*y(4)*y(1);
adaptive = [adaptive(1) adaptive(2) adaptive(3) adaptive(4)]';
```

```
4/25/15 7:25 PM  C:\Users\MADAM HAWA ADUSEI\Documents\MATLAB\cmiadaptive.m          1 of 1

function cmiadaptive =cmaidaptive(t,y)
cmiadaptive(1)=1-1.25*y(1)+0.252*y(1)*y(2)/(1+0.008*y(1)*y(2))+1.20*y(1)*y(3);
cmiadaptive(2) =1-1.25*y(2)+0.252*y(2)*y(1)/(1+0.008*y(2)*y(1))+0.85*y(2)*y(3);
cmiadaptive(43)=0.1*y(3)-1.20*y(3)*y(1)*y(2);
cmiadaptive = [cmiadaptive(1) cmiadaptive(2) cmiadaptive(3)]';
```

REFERENCES

Ackleh, A.S. and L.J.S. Allen, 2003. Competitive exclusion and coexistence for pathogens in an epidemic model with variable population size. J. Math. Biol., 47: 153-168.

Anderson, R.M. and R.M. May, 1992. Infectious Diseases of Humans. Oxford University Press, Oxford pp: 528-530.

Baron, S., 1996. Medical Microbiology. 4th Edn., University of Texas Medical, Galveston, Texas,.

Ben-Shachar, R. and K. Koelle, 2014. Minimal within-host dengue models highlight the specific roles of the immune response in primary and secondary dengue infectionss. R. Soc. Publish. 10.1098/rsif.2014.0886

Bittner, B. and L.M. Wahl, 2000. Immune responses against conserved and variable viral epitopes. J. Theoret. Med., 3: 37-49.

Brauer, F., 1984. Compartmental Models in Epidemiology. University of British Columbia, Vancouver BC., Canada.

Germain, R.N., 1994. MHC-dependent antigen processing and peptide presentation: Providing ligands for T lymphocyte activation. Cell, 76: 287-299.

Hancioglu, B., D. Swigon and G. Clermont, 2007. A dynamical model of human immune response to influenza A virus infection. J. Theoret. Biol., 246: 70-86.

Heffernan J., B. Sahai and R. Smith, 2009. Mathematical immunology of infectious diseases. University of Ottawa.

Iwasa, Y., K. Sato and Y. Takeuchi, 2007. Mathematical Studies of Dynamics and Evolution of Infectious Diseases. In: Mathematics for Life Science and Medicine, Takeuchi, Y., Y. Iwasa and K. Sato (Eds.). Springer, Germany, pp: 1-4.

Long, C., H. Qi and S.H. Huang, 2008. Mathematical modeling of cytotoxic lymphocyte-mediated immune response to hepatitis B virus infection. J. Biomed. Biotechnol. 10.1155/2008/743690

Murray, J.D., 2001. Mathematical Biology II: Spatial Models and Biomedical Applications. 3th Edn., Springer-Verlag, New York,.

Nakata, Y., 2011. Global dynamics of a cell mediated immunity in viral infection models with distributed delays. J. Mathemat. Anal. Applic., 375: 14-27.

Nirvanagrewal, 2012. The two different types of immunity. Medical Science Academy, March 2012. http://www.brighthub.com/science/medical/articles/20937.aspx.

Pawelek, K.A., 2012. Mathematical modeling of virus infections and immune responses. Dissertation of Applied Mathematicis (Virology and Immunology), Oakland University, Oakland, CA., pp: 1-192.

Tian, X. and J. Wang, 2015. Stability analysis for viral infection model with multitarget cells, beddington-DeAngelis functional response and humoral immunity. Discrete Dynamics Nature Soc., Vol. 2015. 10.1155/2015/654507

Wiah, E.N., I.K. Dontwi and I.A. Adetunde, 2011. Using mathematical model to depict the immune response to hepatitis B virus infection. J. Mathemat. Res., 3: 157-167.

Wodarz, D., 2004. Mathematical models of immune effector responses to viral infections: Virus control versus the development of pathology. J. Comput. Applied Math., 184: 301-319.

Wodarz, D., S. Sierro and P. Klenerman, 2007. Dynamics of killer T cell inflation in viral infections. J. R. Soc. Interface, 22: 533-543.