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A Mathematical Model of The Effect of Immuno-Stimulants On The Immune Response To HIV Infection

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Abstract: The success of antiretroviral drugs (ARVs) to control Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) and eliminating the condition depends on the accurate estimation of prognostic indicators of treatment outcomes. Mathematical models using differential equations were formulated to describe the interaction of the Immune system with HIV pathogens. Proliferation rate of naive and HIV specific activated effector cells was investigated to determine the threshold efficacy of immuno-stimulants for perfect immune response. The conditions for the existence and stability of disease free equilibrium (DFE) and endemic equilibrium point (EEP) were determined. It was found that DFE exists if the Reproductive ratio, $R_0 < 1$ and EEP exists when $R_0 > 1$. Epidemiological and demographic parameters of HIV/AIDS and immune response data analyzed showed that in the absence of immuno-stimulants, $R_0 = 4$, and the introduction of immuno-stimulants increased the proliferation rate of effector cells, thus improving the immune response time to eliminate the infection. This means R_0 reduces from $R_0 = 4$ to values less than one. Simulation results with varying efficacy levels of immuno-stimulants showed that the EEP becomes extinct and DFE is stable if the drug efficacy is at $e = 75.4\%$. The results also showed that the normal cell homeostatic rate of $N = 2$ daughter cells is activated by use of immuno-stimulants to increase to multiples of $N = 3.49$ memory cells during a re-emergence of the disease.

Key words: CD4+ cell count, Effector cells, Epidemiology, Immuno-stimulants, Reproductive ratio.

1. Introduction

Mathematical modeling has provided social and science oriented researchers with more knowledge about the real world systems. Mathematical models are used in many disciplines including, natural sciences, engineering, social sciences among others [1]. These models provide a better understanding to the physical components of the systems and allow the researchers to make better predictions about the system's behaviour.

Many mathematical models can take different forms that are either static or dynamic, explicit or implicit, discrete or continuous, deterministic or stochastic (probabilistic), deductive, inductive or floating, linear or non linear [2]. Typically, deterministic models are given in two ways [3]. First, if the data are known at a discrete set of times, then the model is structured as a map, or discrete- time dynamical system. Secondly, if the data can be obtained or interpolated well over any time, then the model is given by differential equations or continuous- time dynamical system [4].

Mathematical models will provide the envisaged results when they have been analyzed. For epidemiological models [5], a common analytical tool is the basic reproductive number or rate or ratio or just R_0. If the model is about the progression of an infectious disease, the reproductive ratio is defined such that if the value is greater than a certain threshold, the disease will persist in a population, but if it is below a certain threshold, the disease will eventually be removed with no external manipulation. Epidemic modeling has three main aims. First, is to understand the spreading mechanism of the disease. Second, is to predict the future course of the epidemic. Third, is to understand how we may control the spread of the epidemic. In order, therefore, to make a reliable model and predictions, to develop methods of control, we must be sure that our model describes the epidemic closely and that it contains all its specific features. Models are typically classified on at least three dichotomous features, state, time and variability. The first two can either be discrete or continuous and the last can be either absent (deterministic) or present (stochastic).

Many mathematical models through the use of differential equations have a long history dating to the times of Malthus, Verhulst, Lotka and Voltera[6]. Although these models give rise to a better understanding of more complicated phenomena, it is becoming clear that models cannot capture the rich variety of the dynamics observed in the natural systems [7]. The possible approach to solve this problem is the use of a system of many

equations. This, in many instances, will suffer the problem of using many parameters that cannot, objectively be determined and hence identifying important components in observed behaviour will be quite difficult.

2. Model Assumptions and Formulation

To have explicit dynamical relationships, we make the following model postulations:

i) The model assumes the existence of cell mediated response (CMI) only and there is no humoral immune response. Cell mediated immunity (CMI) is a type of immune system that is not ready to act until activated by an infection. The humoral immune system is the first line of defense that constitutes soluble components like chemokines and cells like macrophages.

ii) The model assumes that infection is only by one viral strain. It is only concerned with drug sensitive HIV viral strain

iii) The model assumes it is only the CD4+ T and dendritic cells that are infected. Other cells that can be infected include themacrophages

iv) The model assumes that the infection is by mass action principle, where the interaction is a function of interacting populations.$CD4^{+}$cells are infected in proportion of the product of abundances of T cells and viral load.

v) The cells once infected start producing virus, latency period is ignored Model Equations

With the above assumptions and parameters, we formulate the following model to describe the immune response to HIV infection.

Letting T denote the population of activated CD4+ cells, E to denote the population of effector cells and V to denote the population of the viral material, the model equations are given by,

$$\frac{dT}{dt} = s + rT\left(1 - \frac{T}{K}\right) - \mu_T T - (1-e)\beta TV \quad (1)$$

$$\frac{dE}{dt} = N(1-e)\beta TV - \mu_e E \quad (2)$$

$$\frac{dV}{dt} = M(1-e)\beta TV - \mu_V V \quad (3)$$

3. Disease Free Equilibrium Points (DFE)

This is the situation in which the disease is absent in the population and thus infection terms are absent and the remaining population of naïve cells will grow logistically. In the absence of the disease, the value of the population variables $V(t) = 0$ and $E(t) = 0$ are zeros, and therefore the system reduces to;

$$\frac{dT}{dt} = s + rT\left(1 - \frac{T}{K}\right) - \mu_T T = 0 \quad (4)$$

Equating the right hand side to zero and solving for *T* yields the equilibrium point

$$s + rT\left(1 - \frac{T}{K}\right) - \mu_T T = 0 \quad (5)$$

Rearranging the expression above yields a quadratic equation

$$T^2 + \frac{K}{r}(\mu_T - r)T - \frac{Ks}{r} = 0 \quad (6)$$

This can be expressed in the form

$$T^2 + b\mathrm{T} + c = 0 \quad (7)$$

Where $b = \frac{K}{r}(\mu_T - r)$and $c = \frac{-sK}{r}$. Solving the quadratic equation, the value *T* will be

$$T^* = \frac{-b \pm \sqrt{(b)^2 - 4c}}{2} \quad (8)$$

Substituting the values of $b$and c in equation (8) above becomes;

$$T^* = \frac{K}{2r}(r - \mu_T) + \left[\left\{\frac{K}{2r}(r - \mu_T)\right\}^2 + \frac{Ks}{r}\right]^{\frac{1}{2}} \quad (9)$$

The equilibrium point will be;

$$(T^*, V^*, E^*) = \left(-\frac{K}{r}(\mu_T - r) + \left[\left\{\frac{K}{r}(\mu_T - r)\right\}^2 + \frac{4Ks}{r}\right]^{\frac{1}{2}}, 0, 0\right) := DFE \quad (1)$$

4. Endemic Equilibrium points (EEP)

In case the disease persists, there exists an endemic equilibrium point where the disease co-exists in the body with the immune cells. The equilibrium point was obtained by solving the equations 1, 2 and 3 to give

$$s + rT\left(1 - \frac{T}{K}\right) - \mu_T T - (1-e)\beta TV = 0 \quad 11$$

$$s + (r - \mu_T - (1-e)\beta V)T - \frac{r}{k}T^2 = 0 \quad 12$$

$$T^2 - \frac{K}{r}[r - \mu_T - (1-e)\beta V]T - \frac{sK}{r} = 0 \quad 13$$

Eq. 13 can be written in the form

$$T^2 - b_1 T - c_1 = 0 \quad 14$$

where $b_1 = \frac{K}{r}[r - \mu_T - (1-e)\beta V^*]$ and $c_1 = \frac{sK}{r}$.

Therefore the equilibrium point will be

$$T^e = \frac{b_1 + \sqrt{b_1^2 + 4c_1}}{2} \quad 15$$

That is T^e will be given by;

$$T^e = \frac{1}{2}\left\{\frac{K}{r}[r - \mu_T - (1-e)\beta V^e] + \sqrt{\left[\frac{K}{r}[r - \mu_T - (1-e)\beta V^e]\right]^2 + \frac{4sK}{r}}\right\} \quad 16$$

Which can also be expressed as,

$$T^e = \frac{1}{2}\left\{\left\{\frac{K}{r}[r - \mu_T - (1-e)\beta V^e] + \left(\left[\frac{K}{r}[r - \mu_T - (1-e)\beta V^e]\right]^2 + \frac{4sK}{r}\right)^{\frac{1}{2}}\right\}\right. \quad 17$$

From Eq. 2 one may obtain

$$N(1-e)\beta T^e V^e = \mu_e E^e \quad 18$$

Making E^e the subject of the formula in eq. 18 yields;

$$E^e = \frac{N(1-e)\beta T^e V^e}{\mu_e} \quad 19$$

Using eq. 3, the equilibrium is obtained as,

$$N(1-e)\beta T^e V^e - \mu_V V^e = 0 \quad 20$$

Substituting for $V^e = 0$, one obtains the DFE.

If $V^e \neq 0$ then eq. 20 becomes

$$T^e = \frac{\mu_V}{N(1-e)\beta} \quad 21$$

Using eq. 21 in eq. 19 yields,

$$E^e = \frac{\mu_V(1-e)V^e}{(1-e)\mu_e} = \frac{\mu_V V^e}{\mu_e} \quad 22$$

From eq. 1, V^e can be expressed as follows.

$$V^e = \frac{sK + rT^e(K - T^e) - \mu_T T^e K}{K(1-e)\beta T^e} \quad 23$$

From eq. 3 and eq. 23, one obtains

$$V^e = \frac{sN(1-e)\beta + r\mu_V\left(1 - \frac{\mu_V}{KN(1-e)\beta}\right) - \mu_T\mu_V}{\mu_V(1-e)\beta} \quad 24$$

The endemic equilibrium point (EPP) is therefore obtained from equations 21, 22 and 24 as;

$$(\boldsymbol{T^e, E^e, V^e}) = \left(\frac{\boldsymbol{\mu_V}}{\boldsymbol{Ne\beta}}, \frac{\boldsymbol{\mu_V(1-e)V^e}}{\boldsymbol{e\mu_e}}, \frac{\boldsymbol{sN(1-e)\beta + r\mu_V\left(1 - \frac{\mu_V}{KN(1-e)\beta}\right) - \mu_T\mu_V}}{\boldsymbol{\mu_V(1-e)\beta}}\right) \quad 25$$

5. Results and Discussions

Considering the model presented in equation 25, a complete list of parameters and their estimated values that were used for numerical simulations of the model are given in Table 1 below. The majority of the values have been taken from the data found in scholarly articles published in various journals. Much of these parameters were adopted and a complete discussion on their estimation can be found [8-10]. These data do not depict a strict situation of the entire patients range but the parameter range is within the plausible and realistic values. Individuals would have different parameter values but, we modified the parameters to represent a situation in countries in Sub-Saharan Africa of which Kenya is included. Like many countries in this region, the epidemic continues to grow in Kenya as many people become infected each day. Also, many people living with

HIV/AIDS (PLWHA) use ARVs of which in most cases, it is not accessible and/or their adherence is not consistent. Due to this, the amount of drugs taken and therefore their concentration is low. The implication of this is low efficacy and resistance of the viral materials to chemotherapy. In our model, we incorporate parameters which determine the effect of immune boosters on the response to pathogenic invasion.

The variables to be used are assigned initial values at the onset of the disease and parameters used in the model are presented in the table below. Adjustment and modification is however done to the value of parameters to reflect a situation where majority of Kenyan HIV victims fall. In the simulation of the model (eq. 1, 2 and 3), the values of the parameters used are presented in Table 1.

We assume the following initial values in each compartment at the onset of infection to apply.($T(0), E(0), V(0) = 200, 1, 1$), with the health T cells carrying capacity of 1300mm^{-3}.

The following are the values of parameters used.

Table 1Table of Simulation Variables and Parameters

	Parameter description	Symbol	Value	Source
1	Initial population of Naïve T cells	T	200	Approximation
2	Initial population of Effector T cells	E	1	Approximation
3	Population of initial Viral load	V	1	Approximation
4	Intrinsic growth rate of naïve T cell population	r	0.35	Rotich, (2012)
5	Carrying capacity of Naïve T cells per mm^3	K	1300	Perelson, (1993)
6	The natural death rate of Naïve T cells	μ_T	0.025	Perelson, (1993)
7	Force of infection of viral pathogen	β	0.0033	Perelson, (1993)
8	Efficay of Effector T cells in preventing infection	e	$e \in [0,1]$	Calculated
9	Natural death rate of Effector cells	μ_e	0.043	Approximation
10	Multiples of Efector cells produced by each T cell	N	≥ 2	Variable
11	Natural death rate of viral cells	μ_V	1.284	Approximation
12	Burst size of Viral materials	M	5	Approximation
13	Constant Recruitment rate of Naïve CD4+ T cells	s	5	Approximation

In absence of the infection, it is expected that the model representing T cells is a logistic function. Using the parameters and the initial variables listed in Table 1 above, figure 1 was generated using Runge-Kutta numerical scheme of order 4-5 in MATLAB.

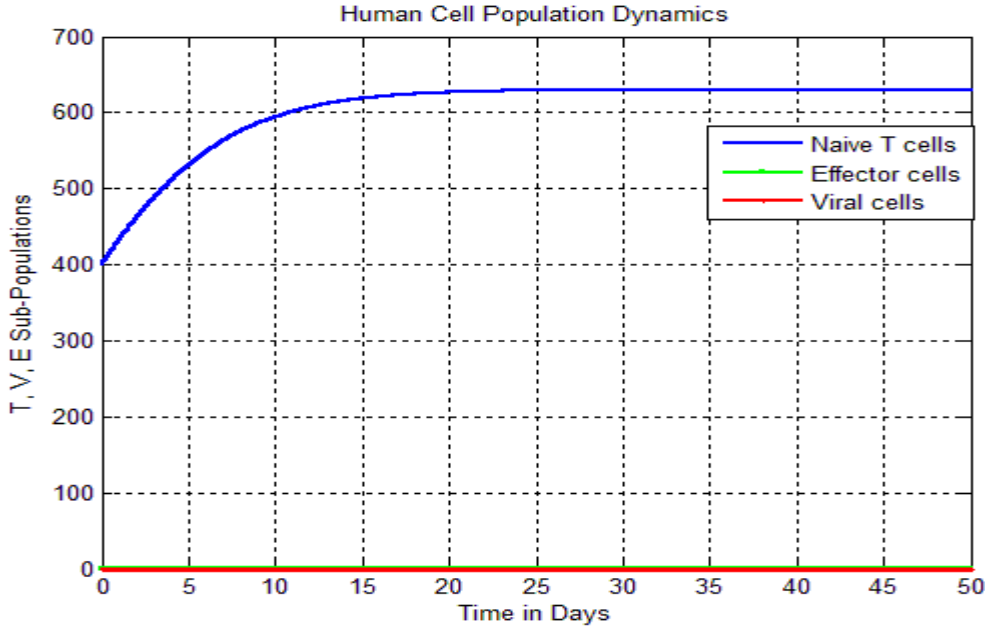

Figure 1 Dynamics of Population of T, E and V in absence of disease.

In figure 1 above, the level of effector cells and the viral materials remains at zero, but the population of naïve T cells grows and stabililizes at carrying capacity.

Figure 2 below shows population dynamics immune system in presence of disease with no intervention.

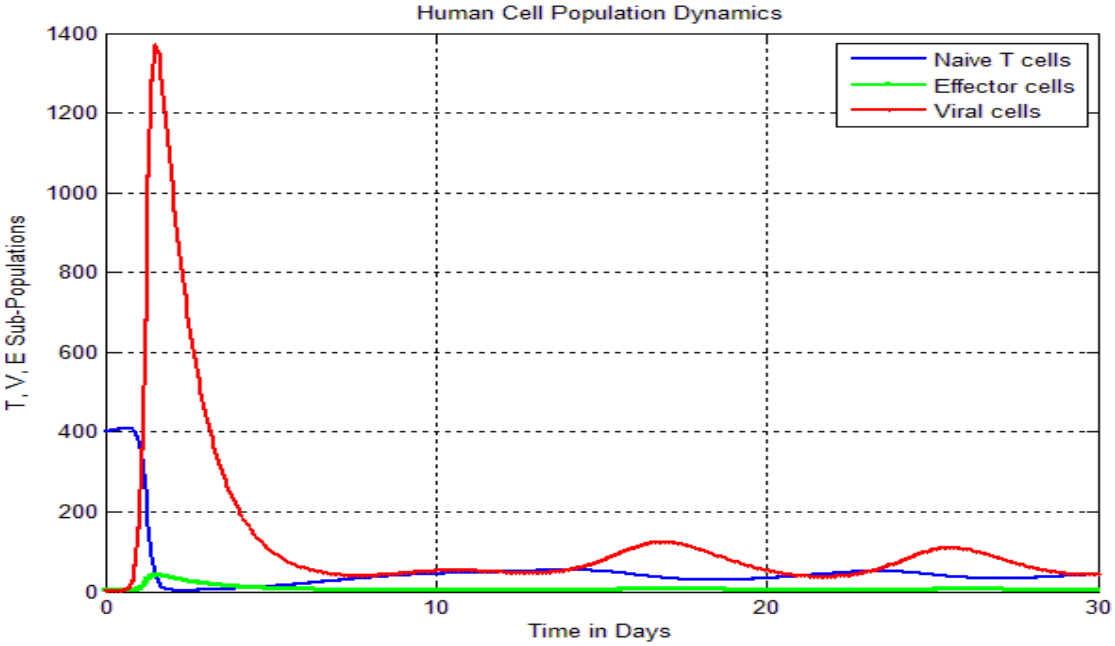

Figure 2 Population dynamics of Immune system in absence of Intervention.

Figure 2 above, the dynamics show a drop in population of Naïve T cells, an increase in effector cells and also an increase in viral materials. The population of viral materials will later fall due to the absence of naïve T cells used to regenerate new viral materials. Immediately after infection, the naïve T cell population drops to almost zero, and at the same time the effector cell population increases. The increase in effector cells is not significant enough to control the population of viral antigens which is noted to rise up to over 1300 parts per mm cube.

Immuno-stimulants increase the production of effector daughter cells. If the immune therapy is given during the disease progression, the response of the effector cells will be faster and at a higher rate. If the immune-stimulants are given before infection, memory cells are formed and made readily available for subsequent attack. We illustrate this phenomenon at the immune-stimulant efficacy of 0.2, 0.5, 0.7 and 0.8 percent respectively. It is noted that as the efficacy is increased, the levels of effector cells against the viral materials is increasing, making the naïve T cells to regenerate and rise to the desired levels.

The graphs for all the levels are compared in Figure 3 below.

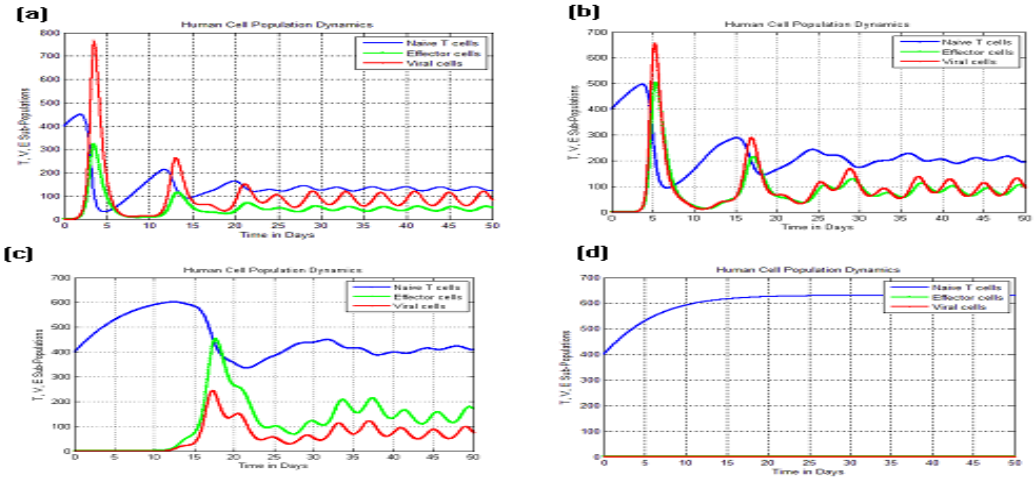

Figure 3 Efficacy of Immune boosters in Population dynamics.

It is worth noting that in Figure 3(d), the graph is similar to the normal dynamics in absence of the disease as shown in Figure 1. This is because the immune system is very effective in eliminating the disease pathogens before much damage is caused.

The immuno-stimulants help improve the efficacy of the effector cells in the immune response. Introduction of immuno-stimulants increases the number of effector cells and thus improves the immune response to pathogenic invasion. The desired levels of the ratio between the effector cells and the virus are represented by the dimensionless parameter R_0. The disease will be eliminated by the system if $R_0 < 1$.

The efficacy level of the immune system to reduce the reproductive ratio to values less than one are simulated in figure 4 using data in Table 1.

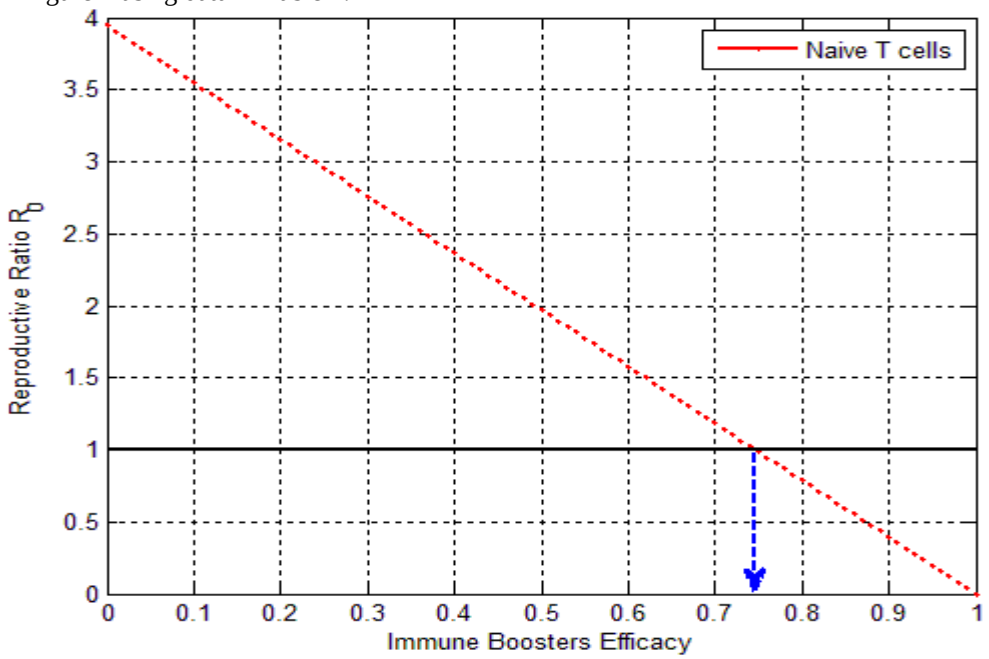

Figure 4. Effects of Immune Boosters on the Reproductive Ratio.

The value of R_0 in the absence of intervention strategy is found to be $R_0 = 4$, which is within the range as indicated in Table 3.1. As the immunostimulants are increased, the levels of R_0 reduces. Clearly, from figure 4, $R_0 \leq 1$ at $e = 0.745$. This means that the production of effector daughter cells is increased by 75% from 2, making $N = 3.49$ which is equivalent to production of daughter cells in 0.57 in unit time. From the numerical analysis above, it is seen that the normal cell population is obtained in Figure 3 (d) at 0.745% drug efficacy.

The desired value of the efficacy is obtained by reading the value on the $x - axis$ that corresponds to $R_0 = 1$. The graph of reproductive ratio versus the immune efficacy is dropping downwards from top left to bottom right as expected. Increase in efficacy leads to a decrease in reproduction of viruses.

6. Conclusion

The HIV/AIDS pandemic and occurrences of other diseases are events of great concern to many people. Epidemics which infect a substantial fraction of the people in some regions or in the whole world have probably been occurring since human beings started living as communities and were well known as plagues. As mathematical epidemiology became a necessary tool in helping provide remedies in disease eradication, complicated medical phenomena could be understood better by using practical modeling techniques. One of this techniques is the use of differential equations to represent phenomena whose dynamics depend on their current state and the state of the system at time t units. Our results were obtained from linearization and by considering the dynamics locally, that is, around fixed points.

The successful use of immuno-stimulants clearly shows that the immunological memory provides protection after re-exposure to an antigen such as HIV. Immunological memory prevents infection after re-exposure in two ways. First, if the magnitude of the immunological memory is sufficiently high, it can render the net growth of the pathogen to be negative. Second, it can prevent some exposures to the pathogen from resulting in productive infection of the host.

A parameter N which was introduced in the model equations to represent the number of T cells responding to the attack by pathogens. The results showed that for unit change in M, the immune boosters are able to reduce

the size of the dimensionless reproductive ratio $R_{o.}$ This was shown by examining the sensitivity of R_o. The results also showed that R_o is very elastic to changes in N. The model system was also shown to be stable at fixed points for both DFE and EEP. The efficacy and efficiency of the immuno-stimulants was also shown to be at 0.754% drug efficacy.

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