Journal of the Nigerian Association of Mathematical Physics
Volume 29, (*March, 2015*), pp 173 – 180

Mathematical Analysis of Controlling Onchocerciasis (Riverblindness)

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Abstract

Control of Onchocerciasis currently focuses on community-directed treatment with the microfilaricide ivermectin which effectively kills Onchocerciasis volvulus microfilariae in the human host. We developed a dynamic SIV compartmental model based on differential equations to propose the analysis of controlling Onchocerciasis. The threshold values give rise to optimism that elimination of Onchocerciasis is feasible, but the associated measures of parasite prevalence and density suggest that Onchocerciasis can remain endemic at very low infection intensities. The existence and stability of the disease-free equilibrium is analyzed. In view of the impact of control efforts,we discovered that elimination of Onchocerciasis is possible, it is important to sustain current control efforts.

Keywords: Onchocerciasis, threshold value, Mathematical model, Equilibrium, Stability, Endemicity, Low Infection Intensities, Ivermectin.

1.0 Introduction

Onchocerciasis (River Blindness) is an insidious non-fatal filarial disease that causes blindness, lifelong human suffering, and grave socioeconomic problems. It's causes a clinical and epidemio-logical burden of skin disease in Africa. It is caused by infection with filarial parasite (Onchocercavolvulus).It causes a high burden of blindness and other (e.g. skin) pathology in severely affected communities. The parasite is transmitted by simulium species (blackflies) that breed in fast owing stream. An estimated 40 million people are afflicted worldwide with about 2 million blind. About85:5 million people in 35 countries live in endemic areas. It is endemic in 28 countries in Africa [1], six countries in the Americas,and in Yemen. Some 18 million people are estimated to be infected(over 99 percent of them living in Africa). In 1875, O'Neill first reported the presence of filarial in 'craw-craw' as Onchocerciasis is called in West Africa. In 1919, Robles described in the French literature an anterior uveitis and keratitis associated with acute and chronic skin changes [1].Budden reported Onchocerciasis as an important cause of blindness in many parts of Northern Nigeria [2].

Onchocerciasis, or river blindness, is caused by infection with the filarial parasite Onchocerca volvulus. The parasite is transmitted by Simulium species (blackflies) that breed in fast flowing streams [3]. Until recently the blindness and skin pathology caused by heavy infections, constituted a major public health problem in many parts of tropical Africa, Yemen, and Latin America. In the West African savannah, the risk of Onchocercal blindness used to be very high along the rivers, where the vector breeds, and blindness could affect up to 50. The fear of blindness resulted in depopulation of the fertile river valleys, and this made Onchocerciasis a major obstacle to socio-economic development in West African savannah regions [1]. Control efforts commenced in 1988with prevalence surveys and pilot treatment project in Kwara State. Mass treatment with ivermectin was initiated in 1991 and extended later to other endemic states with the assistance of UNICEF and other international organizations. And in 1997, Nigeria started receiving support from the African Programme for Onchocerciasis Control (APOC) and commenced usage of the Community Directed Treatment with Ivermectin (CDTI) or a concept from Community Directed Intervention (CDI)[5, 6]. APOC was set up in 1995 to establish within a period of 12 to 15 years, effective and sustainable, community-directed treatment with Ivermectin throughout the endemic areas within the geographic scope of the programme, and, if possible, to eradicate the vector in selected and isolated foci, by using environmentally safe methods. Blackflies (Simulium damnosum) are known not only for their nuisance causing economic losses in different areas of human activities, but also for transmission of pathogens and parasites to man and animals.

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In some areas, blackflies are vectors of a filarial worm (Onchocerca Volvulus) which causes a serious endemic disease whose final stage is known as river blindness. "Onchocerciasis, or river blindness, is one of the major endemic, parasitic diseases which in addition to causing untold human suffering is a major obstacle to socioeconomic development. It is found in the Americas, in the south-western part of the Arabian peninsula and in East, Central and West Africa. Black fly larvae are found at specific breeding sites in rivers since we have to control the mortality level over long distances, we have to take into account the transport, the diffusion and the decay of the larvicide [6, 7]. The behavior of the concentration of larvicide along the river can be modelled by a diffusion transport partial differential equation. Biologists have established that for the types of larvicides used the rate of mortality is proportional to the "dose", the time integral of the concentration up to infinity. Epidemic modeling has three main aims: (1) to understand better the mechanisms by which diseases spread, (2) to predict the future course of the epidemic, (3) to understand how we may control the spread of the epidemic. In this work we deal with all the aims, analyzing impact of pandemic measures (drugs and treatment control) on the spread of Onchocerciasis epidemics in Nigeria. Firstly, we present a brief overview of mathematical epidemiology to understand the development of the theory and to decide how far we can go in order to describe the epidemics as rigorously as it is possible [8,9]. Although we admit that the nature of worm's transmission is stochastic, most of this project work with deterministic models, as it is considered a sufficient approximation and its main advantage is its simpler, but not necessarily simplistic analysis. We want to investigate the expected effect of the pandemic measures on epidemics, dealing with expected behavior of its spread that deterministic models illustrate. In the second section, we decide for the deterministic model that suits the Onchocerciasis [10, 12]. Next section deals with optimal control with drug treatment [13, 14]. In its first part, we assume that vaccines are fully effective and in the second part, we assume their effectiveness to be only 70 per cent. In both cases, we do not look at the problem only from medical perspective, i.e. how vaccination can affect the spread of the disease, but also from economical perspective, i.e. how much we can save when we vaccinate the population. The fourth section follows the methods derived in the previous section and analyzes the impact of drugs suppressing on the spread of the epidemics. We discuss the problem from medical perspective and economical point of view, as well. At the end of the section, taking in consideration the above issues we will address, through mathematical modeling, the possible effects on incorporating such macro filaricidal drug on the control of O.volvulus and provide suggestions on how it should be best used.

2.0 Definition of some common terms in Onchocerciasis

(a) **Force of Infection:** The instantaneous per capital rate at which susceptible hosts become infected; a theoretical measure of the number of new infections arising per unit of susceptible population and per unit time i.e. the instantaneous incidence rate per susceptible host.

(b) **Anthropophily:** A measure of vector preference to feed on humans quantified as the proportion of blood meals of human origin (the human blood index) in vector population samples. It ranges from 0 to 1.

(c) **Vector Competence:** The ability of a vector species to ingest, permit multiplication or development of (or both of these) and transmit a pathogen.

(d) **Vector Complexes:** Closely related vector species that are reproductively isolated yet morphologically indistinguishable, are referred to as cryptic or sibling species.

(e) **Strategic/Tactical models:** Strategic models aim to make simple and transparent frameworks, taking into account a few key biological processes and trying to understand thoroughly how they interact.

(f) **ABR:** Annual Biting Rate (number of vectors take a blood meal on one human host per year)

(g) **ATP:** Annual Transmission Potential [average number of infections larvae(L3) transmitted to one human host per year]

(h) **Breakpoint:** A parasite number or density below which infection cannot persist. Breakpoints can be determined for each parasite stage and also guarantee the existence of a stable zero equilibrium, which is a prerequisite of stable elimination.

(i) **Density-Dependent Processes:** Regulatory processes in the vector-parasite relationship which depend in a non-linear way on the parasite density i.e. the number of parasites per host.

(j) **Transmission threshold:** A threshold variable in vector-borne infections that defines the vector density below which infection cannot persist.

(k) **Super infection:** In the context of filarial diseases, this term is used for describing the process of infection with a new parasite while being already infected with one or more parasites of the same species.

(l) **Parasite Control:** Reduction incidence, prevalence or morbidity to a locally acceptable level. Requires continued interventions and might constitute the first phase of national intervention programme.

(m) **Parasite Elimination:** Reduction of the incidence of infection to zero in a defined geographic area. Requires continued measures to prevent re-establishment of transmission.

(n) **Parasite Eradication:** Permanent reduction to zero of the worldwide incidence of infection. Once accomplished, intervention measures will no longer be required. Ultimate goal of the global programme.

(o) **Endemic:** Habitual presence (usual occurrence) of a disease within a given geographical area; a disease always present.

(p) **Epidemic:** Occurrence of an infectious disease clearly in excess of normal expectancy; sudden outbreak of a disease.

(q) **Pandemic:** Worldwide epidemic affecting exceptionally high proportion of the global population.

3.0 Mathematical Formulation of the Model

4.0 Introduction

The model consists of four ordinary differential equations describing the rate of change with respect to time of the compartment of human susceptible, human infected, vector susceptible and vector infected at time t. There are several various model for describing epidemics with different properties with respect to mortality, immunity and time horizon.

In this section, we consider a standard SIV model with variable total population. Suppose H_S represents the number of susceptible, H_I represents the number of individuals who are infected and V represents the vector (blackflies).It is important to note that this model is applicable to a class of disease that is fatal, despite the availability of treatment and drugs.

5.0 Statement of the Model Formulation

Consider the standard model under the assumption of constant population size. Susceptible individuals become infected either by contact with infected individuals or through contact with infected blackflies. An infected individual thus generates secondary infections in two ways; by shedding the pathogen into the susceptible vector (blackflies) which susceptible individuals subsequently come into contact with it.

In the model to be considered below, we have the following variables and parameters which are:

Hs is the Human Susceptible

H_I is the Human Infected

V_S is the Vector Susceptible

V_I is the Vector Infected

$\xi$is the Movement rate from H_S to H_I

$\alpha$is the Recovery rate from H_I to H_S (proportion of ivermectin/Mectizan treatment successfully cure the patients)

ρ is the Transmission rate parameters for H_I to V_S

δ is the Transmission rate parameters for V_I to H_S

m is the Movement rate from V_S to V_I

μ is the Natural death rate

β is the death rate for vector

$\sigma$is the Artificial death rate (cause as a result of chronic river blindness diseases)

$\psi$is the Recruitment rate of Humans (Immigration rate, Birth rate)

The corresponding model equations to the compartments above are

$$\dot{H}_S = \psi + \alpha H_I - \xi H_S V_I - \mu H_S \quad (1)$$

$$\dot{H}_I = \xi H_S V_I - \alpha H_I - \sigma H_I - \mu H_I - \mu H_I \quad (2)$$

$$\dot{V}_S = \rho H_I - m V_S - \beta V_S \quad (3)$$

$$\dot{V}_I = m V_S - \beta V_I - \delta V_I \quad (4)$$

Where

$$H_S(0) = H_{S_0}, H_I(0) = H_{I_0}, V_S(0) = V_{S_0}, V_I(0) = V_{I_0}$$

At the critical point / equilibrium state

$$\dot{H}_S(t) = 0\,, \dot{H}_I(t) = 0, \dot{V}_S(t) = 0, \dot{V}_I(t) = 0 \quad (5)$$

By re-scaling the system of the model (1) to (4) gives dimensionless variables. Let

$$H_S(t) = w\,, H_I(t) = r, V_S(t) = y\,, V_I(t) = z \quad (6)$$

The rescaled system is as follows

$$\psi + \alpha \; - \xi \quad - \mu \quad = 0 \quad (7)$$

$$\xi \quad - \alpha \; - \sigma \; - \mu \; - \rho \; = 0 \quad (8)$$

$$\rho \; - m \; - \beta \; = 0 \quad (9)$$

$$m \; - \beta \; - \delta \; = 0 \quad (10)$$

solving the system of the model equations in equation (7) to (10) for the diseases free equilibrium state. Therefore the diseases free equilibrium is

$$\varepsilon_0 = \left(\frac{\psi}{\mu}, 0,0,0\right) \quad (11)$$

also the endemic equilibrium state becomes:

$$\varepsilon_1 = (w^*, r^*, y^*, z^*) \quad (12)$$

where

$$w^* = \left(\frac{(\alpha+\sigma+\mu+\rho)(m+\beta)(\beta+\delta)}{\xi_f}\right)$$

$$r^* = \left(\frac{(m+\beta)(\beta+\delta)(\mu(\alpha+\sigma+\mu+\rho)(m+\beta)(\beta+\delta)-\psi\quad)}{\xi_f\quad(\alpha(m+\beta)(\beta+\delta)+\delta\quad-(\alpha+\sigma+\mu+\rho)(m+\beta)(\beta+\delta))}\right)$$

$$y^* = \frac{(\beta+\delta)}{m}\left(\frac{\mu(\alpha+\sigma+\mu+\rho)(m+\beta)(\beta+\delta)-\psi\quad)}{\xi(\alpha(m+\beta)(\beta+\delta)+\delta\quad-(\alpha+\sigma+\mu+\rho)(m+\beta)(\beta+\delta))}\right)$$

$$z^* = \left(\frac{\mu(\alpha+\sigma+\mu+\rho)(m+\beta)(\beta+\delta)}{\xi(\alpha(m+\beta)(\beta+\delta)+\delta\quad-(\alpha+\sigma+\mu+\rho)(m+\beta)(\beta+\delta))}\right)$$

$$R_0 = \left(\frac{\rho}{\mu(\alpha+\sigma+\mu+\rho)(m+\beta)(\beta+\delta)}\right)$$

Theorem 2.1: Given a system of equations (1) to (4) there exists a threshold number Ro that helps to determine whether an outbreak of Onchocerciasis occurs with Ro given by:

$$R_0 = \left(\frac{\rho}{\mu(\alpha+\sigma+\mu+\rho)(m+\beta)(\beta+\delta)}\right)$$

Proof of 2.1. We differentiate the system of equations (7) to (10) with respect to (w; r; y; z)to get Jacobian matrix, then we obtain the characteristic equation from the Jacobian determinant where

$$R_0 = \left(\frac{\rho}{\mu(\alpha+\sigma+\mu+\rho)(m+\beta)(\beta+\delta)}\right)$$

Hence, the basic reproduction Ro is computed using the next generation matrix approach or by simply imposing the non-negativity condition on the infected compartment H_f. Ro is the average

number of secondary infections produced when one single infected individual is introduced into a host population where everyone susceptible. Note that our Ro above is a product of the average number susceptible per unit time (in the presence of drugs and possibility of natural death) and the rate of the disease transmission by an infective over the period of his / her infectivity. It is indeed a threshold quantity that helps to determine whether an outbreak of infectious disease dies out or spreads in a community when Ro< 1; the disease die out without any medical interventions but when Ro> 1,the disease becomes endemic and this necessitates the introduction of some control measures in order to curtail the situation. Then we investigate the stability of the disease free equilibrium by examine the behaviour of the model.

6.0 Local Stability of the Equilibrium

Theorem 2.2: The disease free equilibrium is locally asymptotically stable if Ro< 1

Proof of 2.2: The Jacobian matrix J of the system equation. Evaluating matrix J_0 at the disease free equilibrium gives since $|J_0 - I_\cdot| = 0$ then it follows that,

$$-(\mu + \lambda)\left[(-(\alpha+\sigma+\mu+\rho+\lambda)\times-(m+\beta+\lambda)(\beta+\delta+\lambda)) + \left((\xi\frac{\Psi}{\mu})\rho m\right)\right] = 0$$

therefore,

$$-(\mu+\lambda) = 0$$

or

$$\left[(-(\alpha+\sigma+\mu+\rho+\lambda)\times-(m+\beta+\lambda)(\beta+\delta+\lambda)) + ((\xi\frac{\Psi}{\mu})\rho m)\right] = 0$$

Thus, the matrix J_0 has one of its eigenvalues to be

$\lambda_1 = -\mu$

Let $a = (\alpha+\sigma+\mu+\rho)$, $b = (m+\beta)$, $c = (\beta+\delta)$

$\lambda^3 + (a+b+c)\lambda^2 + (a\ +a\ +b\ )\lambda + a\quad - \xi_f\quad\left(\frac{\psi}{\mu}\right) = 0$ (13)

Also, let $d = (a+b+c)$, $e = (a\ +a\ +b\ )$, $a\quad f = a\quad - \xi_f\quad\left(\frac{\psi}{\mu}\right)$

Then equation (13) becomes

$\lambda^3 + d\lambda^2 + e\ + f = 0$

Using Descartes' sign rule: counting sign changes tells us how many positive and negative real zeroes we might have

[1] For the polynomial $\lambda^3 + d\lambda^2 + e\lambda + f$ there is no sign change as indicated. This means there is no real positive zero;

[2] Substitute (λ) for λ and repeat the process. $\lambda^3 + d\lambda^2 + e\lambda + f$

$$-\lambda^3 + d\lambda^2 - e\lambda + f$$

There are now three sign changes. This means that at most there are three negative real zeroes. So, the possibilities are: Note that we could have only an even number of complex zeros because the coefficients of the polynomial are real (you need conjugate pairs for that to happen).Since there is no positive root and we have three negative roots or three complex roots. Thus, the disease free equilibrium is locally asymptotically stable. For the local asymptotic stability, we require

$$\left(\frac{\rho\xi\Psi m}{(\alpha+\sigma+\mu+\rho)(m+\beta)(\beta+\delta)}\right) = R_0 < 1$$

Thus the disease free equilibrium $_0$ is locally asymptotically stable if Ro < 1.

Remark 2.1: The case Ro = 1 is a critical threshold point where the disease free equilibrium $\epsilon_0$loses its asymptotic stability and simply becomes (neutrally) stable. Moreover, it becomes unstableimmediately Ro > 1 and this will lead to the existence of a stable endemic equilibrium ϵ_1.Note that Ro = 1can literarily be viewed as a transcritical bifurcation point where stability is exchanged between ϵ_0 and ϵ_1

Theorem 2.3. The endemic equilibrium is locally asymptotically stable if all the eigen values are negatives.

Proof of 2.3. The Jacobian matrix J evaluated at the endemic equilibrium gives

$$J_1 = \begin{pmatrix} -(\mu) & \alpha & 0 & (\delta - \xi w^*) \\ \xi z^* & -(\alpha+\sigma+\mu+\rho) & 0 & \xi w^* \\ 0 & \rho & -(m+\beta) & 0 \\ 0 & 0 & m & -(\beta+\delta) \end{pmatrix}$$

Let$p = (\xi z^* + \mu),\ q = (\delta - \xi w^*),\ r = (\alpha+\sigma+\mu+\rho),\ s = (m+\beta),\ t = (\beta+\delta), \mu = \xi z^*,\ v = \xi w^*$

Thus the eigen values are

$\lambda_1 = -p$

$\lambda_2 = -(p\ -\alpha\ )$

$\lambda_3 = -(\alpha\ -p\ )$

$\lambda_4 = -\left(s\ (\alpha\ -p\ ) + m\ (p\ +u\ )\right)$

Then $\lambda_1 < 0, \lambda_2 < 0$ $i.e.$ $(p\ > \alpha\ ), \lambda_3 < 0$ $i.e.$ $(\alpha\ > p\ ), \lambda_4 < 0$ $i.e.$ $(\alpha\ -p\ > 0)$

Thus the endemic equilibrium is locally asymptotically stable.

7.0 Simulation Results and Discussion

Numerical solutions of the system

$$\begin{aligned} \dot{w} &= \psi + \alpha\ -\xi\ -\mu\ +\delta \\ \dot{r} &= \xi\ -\alpha\ -\sigma\ -\mu\ -\rho \\ \dot{y} &= \rho\ -m\ -\beta \\ \dot{z} &= m\ -\beta\ -\delta \end{aligned} \tag{14}$$

Where

$$w(0) = w_0,\ r(0) = r_0,\ y(0) = y_0,\ z(0) = z_0 \tag{15}$$

are executed using MAPLE with the following hypothetical parameter values and initial conditions:

$$\xi = 0.2192\ \ \alpha = 0.1027\ \ \beta = 0.0357\ \ \rho = 0.2841\ \ \delta = 0.1369\ \ \mu = 0.0506\ \ \sigma = 0.007\ \ \Psi = 0.2568\ \ m = 0.2841\ \ w_0 = 0.5\ \ r_0 = 0.5\ \ y_0 = 0.5\ \ z_0 = 0.5 \tag{16}$$

In this section, the system has been solved numerically, and the results have been presented. In this formulation, there were initial conditions for the state variables and terminal conditions for the adjoints. That is, the optimality system is a two-point boundary value problem, with separated boundary conditions at times t = 0 and t = T. So the aim is to solve this problem for the value T = 12. This value was chosen to represent the time in years at which treatment is stopped. It is important to note that the parameters values above where chosen such that the total population never goes into extinction and it yields $R_0 > 1$ in the absence of drugs and treatment controls. In the figure 1,we display numerical solution for our model H_S,H_I and V_I compartments with control weights(A = 3,B = 1,C = 1),(A = 1,B = 3,C = 1) and(A = 1,B = 1,C = 3),(A = 2,B = 2,C = 2),(A = 3,B = 2,C = 2) respectively. We observe that, we mostly use less of control with the bigger weight and more of the control with the lesser weight. However, in the case where both weights are equals, initially we have to apply more of drugs control to reduce the susceptible to below certain threshold, after which we gradually start to apply more of the treatment control with less of the drugs. The result show that applying more of the drugs does not appreciably bring down the number of infected individuals as compared to the case when we applied more of treatment control which makes the infected

compartment to peak down. In figure 2, we display numerical solution for our model compartments with no control weights. We observe that the human susceptible reduces while there is rapid increase in human infected and vector infected. However, the peak attained in the latter case does not seem to be significantly different from the case when the two controls are equally weighted.

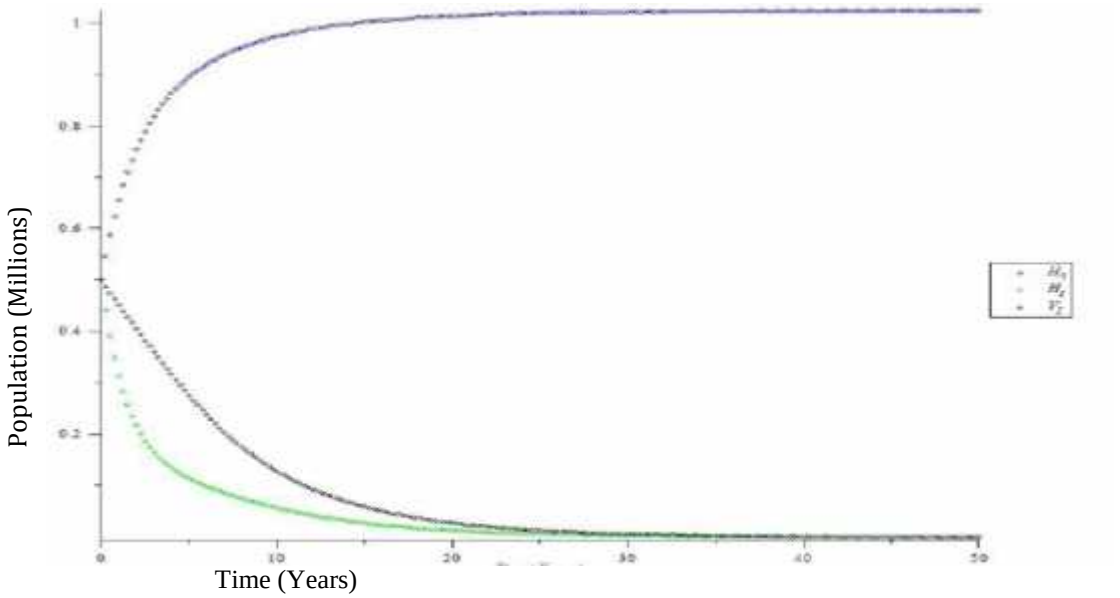

Figure 1: Size of the total population over time for system (14) with parameters (16) and initial conditions (15). Putting controls on Human Susceptible (H_S), Human Infected (H_I), and Vector Infected (V_I)

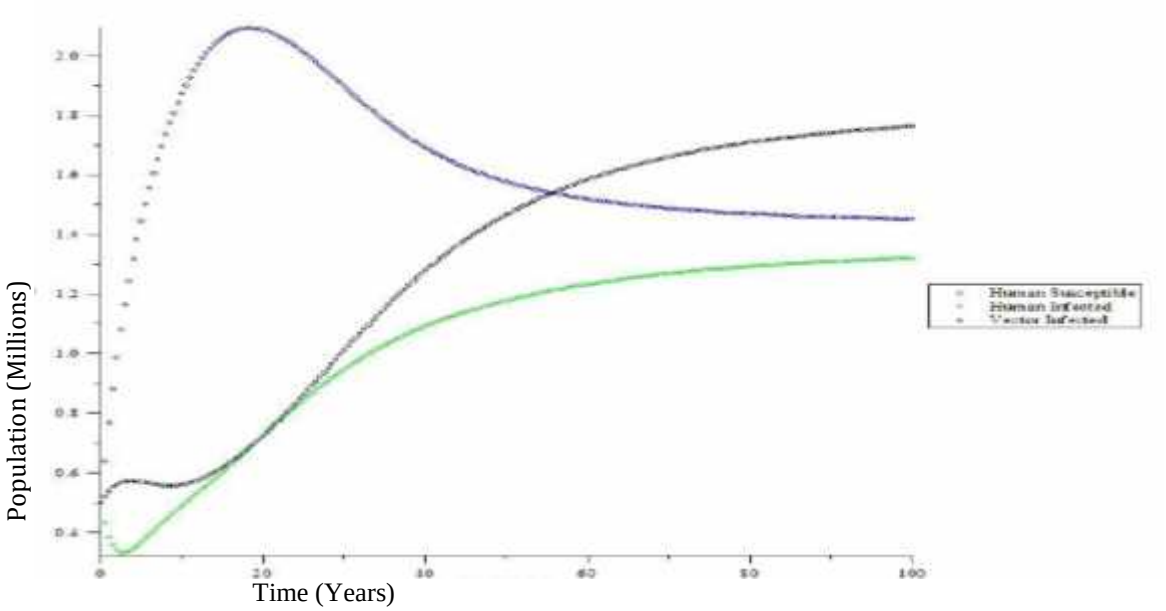

Figure 2; Size of the total population over time for system (14) with parameters (16) and initial conditions (15). Putting controls on neither Human Susceptible (H_S), nor Human Infected (H_I), nor Vector Infected (V_I)

8.0 Concluding Remarks

In this work, we studied optimal combination of drug and treatment strategies for driving infectious diseases with cure towards eradication within a specified period. We considered an SIV model with varying size population using drugs, treatment as control measures. We established the conditions for the local stability of the model equilibrium. Numerical simulations of the resulting system showed that, in the case where it is more expensive to treat with drugs than to treat with

resources, resources should be invested in treating the disease until the disease prevalence begins to fall. This option however does not reduce the number of susceptible quickly enough, thus resulting in an overall increase in the infected population. Nevertheless, the case where both measures are equally expensive showed that the optimal way to drive the endemic towards eradication within the specified period is to use more of treatment control initially than drug control to drive the endemic to below certain threshold after which we can then apply less of drug control and more of the treatment control.

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