

## Numerically quantifying the impact of failure to complete treatment on the transmission dynamics of Human-Blackfly Onchocerciasis.

O. OLOWU\*, D. OKUONGHAE, I. AKO and R. OMOREGIE

*Department of Mathematics, University of Benin, Benin City, Nigeria*

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### Abstract

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*Ivermectin is the standard medical intervention prescribed by the World Health Organization for the treatment of Human-Blackfly Onchocerciasis. This treatment is supposed to be administered twice yearly for between ten to fifteen years. This paper numerically examined the effect of unsuccessful treatment on transference dynamics of Human-Blackfly Onchocerciasis in the human society. The numerical study of the Human-Blackfly Onchocerciasis transmission model showed that the fraction of humans who exhaust their scheduled medical intervention as well as the proportionate transference of confirmed cases who unsuccessfully exhausted their medical intervention have important effect on the dynamics of Human-Blackfly Onchocerciasis in a population. Specifically, it was observed that a serious elevation in the fraction of humans who did not exhaust their standard medical intervention has serious effect on the backward bifurcation spectrum. Furthermore, it was again observed that in the process of boosting the rate of medical intervention of confirmed cases, it is also necessary to implement regulation strategies that would spur infected persons to endure the course of medical intervention and that the inability to sustain this will jeopardize the benefits of enhanced rates of medical intervention.*

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**Keywords:** NTDs, Onchocerciasis, Failed treatment, Quantifying, Numerical simulation.

### 1. INTRODUCTION

Human-Blackfly Onchocerciasis (also known as River Blindness) is amongst the 17 abandoned diseases of tropical origin (NTDs) classified and prioritized by World Health Organization (WHO) of which thirteen of these NTDs are intermittent in the geographical expression beneath the Sahara on the African

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\*Corresponding author, e-mail: [oghenewaire.olowu@uniben.edu](mailto:oghenewaire.olowu@uniben.edu)

continent, Asia with certain districts in the Americas (Chitsulo, *et al.* (2000), Hotez and Kamath (2009)). These diseases including the Human-Blackfly Onchocerciasis have wreaked havoc on poor countries of the world. Death from these diseases is estimated to be in the neighbourhood of about one hundred and forty-two thousand deaths in 2013 alone, which of course came down from two hundred and four thousand deaths in 1990 (Chitsulo, *et al.* (2000), Njepuome (2009)).

Clinical solutions aimed at arresting the ugly trend have been conducted severally but these diseases have defied such efforts. Mathematicians have also contributed their quota by building and analyzing Mathematical models aimed at answering explicit open questions designed to unravel the kinetics of these maladies ravishing destitute sweltering nations of the world (see Akhaze and Olowu (2021a), Akhaze *et al.* (2021b), Bada *et al.* (2021), Chiyaka *et al.* (2010), Chiyaka and Garira (2009), Jubril and Ibrahim (2011), Oguoma and Mbah (2014), Omade *et al.* (2015), Omondi *et al.* (2017), Omondi *et al.* (2018), Olowu and Nwankwo (2023), Olowu and Ako (2023), Olowu, *et al.* (2021a), Olowu *et al.* (2021b), Olowu *et al.* (2024), Poolman and Galvani (2006), Basanez and Ricardez-Esquinca (2001)).

Several Mathematical works have been done as regards the dynamics of onchocerciasis but none has numerically studied the outcome of unsuccessful treatment on the transference kinetics of Human-Blackfly Onchocerciasis (see Oguoma and Mbah (2014), Omade *et al.* (2015), Omondi *et al.* (2017), Omondi *et al.* (2018), Olowu and Nwankwo (2023), Olowu and Ako (2023), Olowu, *et al.* (2021a), Olowu *et al.* (2021b), Olowu *et al.* (2024), Poolman and Galvani (2006), Basanez and Ricardez-Esquinca (2001)).

A few of these contributions are as seen in Omondi *et al.* (2017), where they constructed a model that mathematically examined both established and non-established mass drug management with the drug Ivermectin. Thresholds for eradication,  $\mathcal{R}_0$  were determined. Their results revealed that: (i) disease eradication cannot be achieved without reducing the transmission levels to the barest minimum or engaging in serious and effective vector control, (ii) the disease can be controlled but not completely eradicated with treatment at established intervals and (iii) treatment at non established patterns may result to disease outbreak. Also, Omade *et al.* (2015) modeled the dynamics of Onchocerciasis using an SIR disease modelling pattern with demography in Mubi settlement of Gombe state, Nigeria. In their model, they assumed, (i) dynamic population pattern, (ii) constant recruitment into the untainted class is solely by birth and (iii) that the disease does not confer any form of immunity on susceptible and recovered individuals. Their results suggested that within about 14 days period, 52% of the Mubi residence were at risk of the disease and about 50% tainted rate was recorded among the residence. Recovery rate was reported to be about 37% and that the disease constituted a serious risk to the community.

This paper however focusses on providing numerical answers on quantifying the outcome of unsuccessful treatment on the transmission kinetics of Human-Blackfly Onchocerciasis. Investigating the impact of failed treatment became necessary since the prescribed treatment, ivermectin, for Onchocerciasis by the WHO is to be administered for a minimum of once annually within 10 - 15 years (WHO, 2018). Ivermectin, also called Mectizan, is supposed to be orally served a 12mg maximal dose in a 6 - 12 month cycle till the signs of the infection totally fizzles out (CDC, 2015). Due to the length of time it takes for treatment, certain persons infected persistently breach the treatment protocol within the time frame allotted, thus serving as cannon fodder for disease spread.

## 2. MATERIALS AND METHOD

### 2.1. Mathematical Model

The model, which is mathematical in outlook, to be numerically determined herein is as observed in Olowu *et al.* (2024). The Human-Blackfly Onchocerciasis Mathematical model which incorporates parameter representing failed treatment which we seek to numerically analyze is given by:

The total human populace and that of black flies for all time  $t$  are given respectively by:

$$N_H(t) = S_H(t) + E_H(t) + I_H(t) + T_F(t) + T_C(t)$$

and

$$N_V(t) = S_V(t) + E_V(t) + I_V(t). \tag{1}$$

The model is expressed by the following deterministic, system of nonlinear ODEs (ordinary differential equations):

$$\begin{aligned} S_H &= \Lambda_H - \frac{\beta_H I_V}{N_H} S_H + \sigma T_C - \mu_H S_H, \\ E_H &= \frac{\beta_H I_V}{N_H} S_H - (\alpha_H + \mu_H) E_H, \\ I_H &= \alpha_H E_H + \gamma T_F - (\tau + \delta + \mu_H) I_H, \\ T_F &= (1 - p)\tau I_H - (\gamma + \mu_H) T_F, \\ T_C &= p\tau I_H - (\sigma + \mu_H) T_C, \\ S_V &= \Lambda_V - \frac{\beta_V (I_H + \eta T_F)}{N_H} S_V - \mu_V S_V, \\ E_V &= \frac{\beta_V (I_H + \eta T_F)}{N_H} S_V - (\alpha_V + \mu_V) E_V, \end{aligned} \tag{2}$$

$$I_V = \alpha_V E_V - \mu_V I_V.$$

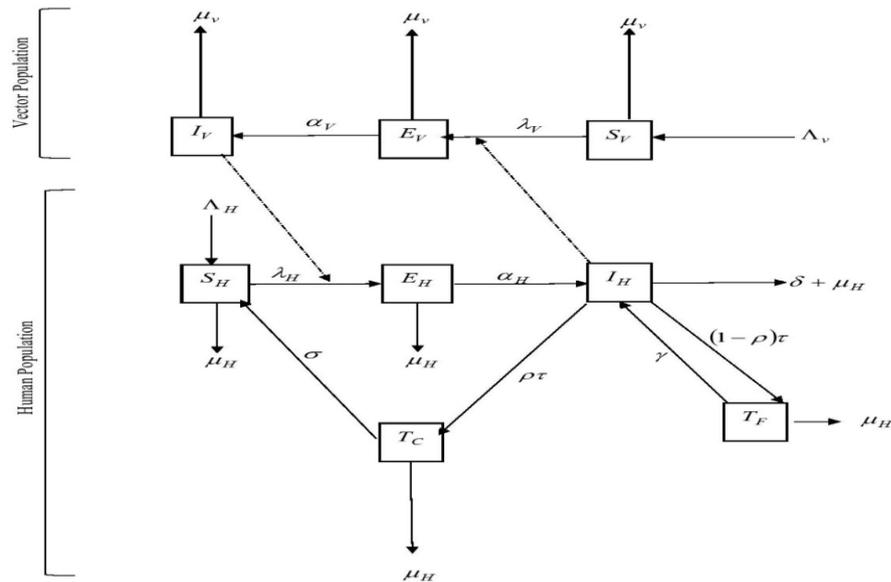
The variables and parameter interpretations are respectively given in Tables 1 and 2, respectively. The transmission kinetics of the Human-Blackfly Onchocerciasis schematics of model in (2) is seen in Figure 1.

**Table 1:** Variable interpretation.

Variable	Description
$S_H$	Population of susceptible individuals
$E_H$	Exposed (latent) individuals
$I_H$	Infectious individuals
$T_F$	Individuals with failed (incomplete) treatment
$T_C$	Individuals who completed treatment
$S_V$	Susceptible vectors
$E_V$	Exposed (infected) vectors
$I_V$	Infectious vectors

**Table 2:** Parameter description of model (2).

Parameter	Description
$\Lambda_H$	Human recruitment rate
$\tau$	Therapeutic rate
$\mu_H$	Natural mortality rate for humans
$\alpha_H$	Progression rate from $E_H$ to $I_H$
$\delta$	Infection-inflicted mortality
$\mu_V$	Natural vector mortality rate
$\alpha_V$	Progression rate from $E_V$ to $I_V$
$\eta$	Parameter which modifies the measurement of the proportionate ability of individuals in class $T_F$ to cause new cases relative to those in $I_H$ ( $0 \leq \eta \leq 1$ )
$\gamma$	Proportion of treated individuals who completed treatment
$\sigma$	Rate at which individuals who failed treatment become re-infected
$\Lambda_v$	Recovery rate
$\beta_H$	Vector recruitment rate
$\beta_V$	Human infectious rate.



**Figure 1:** Schematics of the transmission kinetics of model (2).

### 2.1 Results obtained in OLowu, *et al.* (2024).

We review some results obtained from Olowu, *et al.* (2024). The following are results obtained from Olowu, *et al.* (2024).

1. It was established that the trajectories  $A(t) = (S_H, E_H, I_H, T_F, T_C, S_V, E_V, I_V)$  of the Human-Blackfly Onchocerciasis model with failed treatment parameter and non-negative initial condition will be non-negative for all time  $t > 0$ .

2. The trajectories of Human-Blackfly Onchocerciasis model  $S_H, E_H, I_H, T_F, T_C, S_V, E_V, I_V$  with original conditions and the biological reasonable region is expressed by the set  $D = D_H \times D_V \subset R_+^5 \times R_+^3 \subset R_+^8$  where:

$$D_H = \left\{ (S_H, E_H, I_H, T_F, T_C) \in R_+^5 : N_H \leq \frac{\Lambda_H}{\mu_H} \right\} \quad D_V = \left\{ (S_V, E_V, I_V) \in R_+^3 : N_V \leq \frac{\Lambda_V}{\mu_V} \right\} \quad (3)$$

And that these sets are positively-invariant and serve as attractors for all the non-negative orbits of model (2).

3. Employing the next generation matrix operator method espoused by van den Driessche and Watmough (2002) and deploying notations congruent to the ones applied in van den Driessche and Watmough (2002), Olowu *et al.* (2024) derived the reproduction number as:

$$R_0 = \sqrt{R_{0H} \cdot R_{0V}}$$

where, 
$$R_{0H} = \frac{\beta_H \alpha_H \mu_H ((1-p)\eta\tau + p_3)}{p_1(p_2 p_3 - (1-p)\gamma\tau)\Lambda_H}, \quad R_{0V} = \frac{\beta_V \alpha_V \Lambda_V}{p_5 \mu_V^2}$$

$$p_1 = \alpha_H + \mu_H, p_2 = \tau + \delta + \mu_H, p_3 = \gamma + \mu_H, p_4 = \sigma + \mu_H, p_5 = \alpha_V + \mu_V \quad (4)$$

4. The Endemic Equilibrium Point (EEP) of the model was given as:

$$E_1 = (S_H^{**}, E_H^{**}, I_H^{**}, T_F^{**}, T_C^{**}, S_V^{**}, E_V^{**}, I_V^{**})$$

$$\begin{aligned} S_H^{**} &= \frac{p_1 p_4 G_1 \Lambda_H}{\lambda_H^{**} G_2 + p_1 p_4 \mu_H G_1}, & E_H^{**} &= \frac{p_4 G_1 \lambda_H^{**} \Lambda_H^{**}}{G_2 \lambda_H^{**} + p_1 p_4 \mu_H G_1} \\ I_H^{**} &= \frac{\alpha_H p_3 p_4 \lambda_H^{**} \Lambda_H^{**}}{G_2 \lambda_H^{**} + p_1 p_4 \mu_H G_1}, & T_F^{**} &= \frac{(1-p)\tau \alpha_H p_4 \lambda_H^{**} \Lambda_H^{**}}{G_2 \lambda_H^{**} + p_1 p_4 \mu_H G_1}, \\ T_C^{**} &= \frac{p\tau \alpha_H p_3 \lambda_H^{**} \Lambda_H^{**}}{G_2 \lambda_H^{**} + p_1 p_4 \mu_H G_1}, & S_V^{**} &= \frac{\Lambda_V}{\lambda_V^{**} + \mu_V} \\ E_V^{**} &= \frac{\lambda_V^{**} \Lambda_V}{p_5 (\lambda_V^{**} + \mu_V)}, & I_V^{**} &= \frac{\alpha_V \lambda_V^{**} \Lambda_V}{p_5 \mu_V (\lambda_V^{**} + \mu_V)} \end{aligned} \quad (5)$$

where  $G_1 = p_2 p_3 - \gamma \tau (1 - p) > 0$ ,  $G_2 = p_1 p_4 G_1 - \sigma p \tau \alpha_H p_3 > 0$ .

Placing the expressions in (5) into the infection force, it follows (after multiple manipulations) that the EEP of the model (2) satisfies the polynomial below at the equilibrium point:

$$A_2 \lambda_H^{**2} + A_1 \lambda_H^{**} + A_0 = 0 \quad (6)$$

where,

$$\begin{aligned} A_2 &= p_5 \Lambda_H \mu_V (G_1 p_4 \mu_V + p_4 (1 - q) \alpha_H (\beta_V \eta + \mu_V) \tau \\ &\quad + p_3 \alpha_H (p_4 (\beta_V + \mu_V) + p \mu_V \tau)) (G_1 p_4 + \alpha_H (p_4 (1 - p) \tau + p_3 (p_4 + p \tau))) \\ A_1 &= 2 G_1 p_1 p_4 p_5 \Lambda_H \mu_V^2 (G_1 p_4 + \alpha_H (p_4 (1 - p) \tau + p_3 (p_4 + p \tau))) \\ &\quad + G_1 p_1 p_4^2 p_5 \beta_V \Lambda_H \mu_V \alpha_H (p_3 + (1 - p) \eta \tau) \\ &\quad - G_2 p_4 \alpha_H \alpha_V \beta_H \beta_V \Lambda_V (p_3 + (1 - p) \eta \tau), \\ A_0 &= \Lambda_H \mu_V^2 p_1^2 p_4^2 p_5 G_1^2 (1 - R_0^2). \end{aligned}$$

are the coefficients of the polynomial in (6).

The endemic equilibrium components are thus derived by solving for  $\lambda_H^{**}$  from (6), and placing only the positive values of  $\lambda_H^{**}$  into the equations in (5).

Furthermore, the number of positive roots of (6) is dependent on the number of sign change observed between  $A_1$  and  $A_0$ .

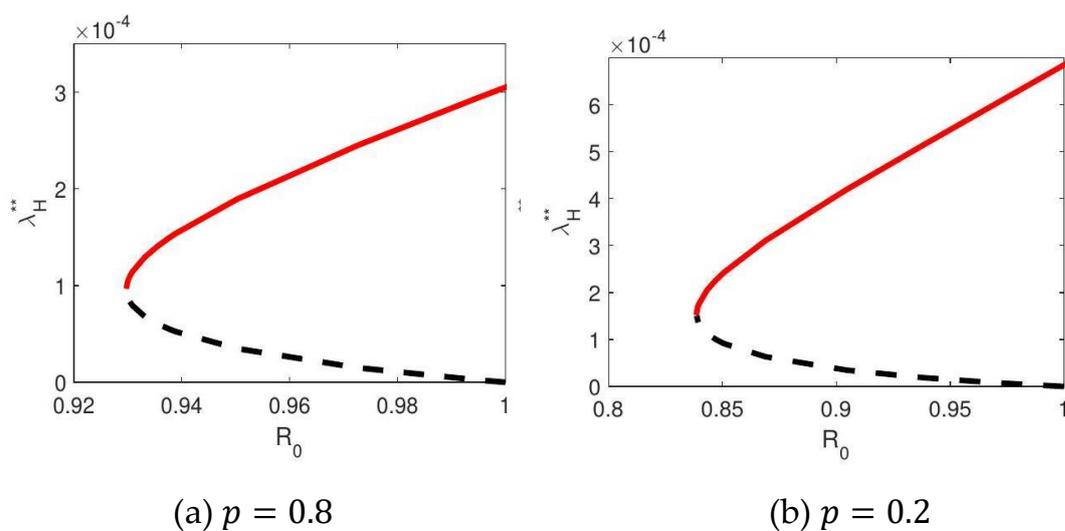
The results obtained above are expressed in the theorem beneath.

5. Backward Bifurcation Phenomenon: Theorem 3.1 The model (2) possesses

- i) dual endemic equilibria if  $A_1 < 0$  and  $R_0 < 1$ ,
- ii) a unique endemic equilibrium if  $A_1 > 0$  and  $R_0 > 1$ ,
- iii) no endemic equilibrium otherwise, when  $R_0 < 1$ .

Based on Item i) of Theorem 3.1 above is indicative of the realistic existence of a backward bifurcation in (2). The backward bifurcation paradox is designated by the co-existence of an infection-free malady state as well as an endemic steady state, with both stable with the condition that the resultant reproduction number falls beneath one. The conclusion is that the standard prerequisite for infection regulation (i.e.,  $R_0 < 1$ ) does not suffice anymore for effective infection regulation in a populace, albeit a necessity. Thus, effective organized plans for infection control will now be consequent upon the initial states of various compartments of the system under consideration (Mishra *et al.* (2010). In a community (wherein people unsuccessfully exhausted the regimen for medical intervention as a result of the extensive duration it demands), the classical condition necessitating the reproduction number being below unity, while a necessity, no longer suffices for successful Onchocerciasis control.

Howbeit this investigation has firmly established that subsistence of onchocerciasis-inflicted mortality will produce a backward bifurcation in the transference kinetics of the disease, the effect of the proportion of cases who successfully exhausted their medical intervention on the bifurcation spectrum. A graphical depiction of the backward bifurcation spectacle expressed in Figure 2 reveals that a reduction in the fraction of cases who successfully exhausted the prescribed medical intervention elevates the backward bifurcation spectrum, causing disease regulation to be even more difficult. Therefore, public health regulation blueprints must not be fixated on boosting medical intervention rates *per se* but also in ensuring that an appreciable percentage of cases with medical intervention successfully exhaust their medical intervention.



**Figure 2:** A graphical representation of backward bifurcation for model (2), showing infection force plotted against the reproduction number  $R_0$  evaluated at  $\tau = \delta = 0.0005$ .

## 6. Global stability of the Disease-Free Equilibrium (DFE) when $\delta = 0$

Every orbit of the mathematical statements of (2), with  $\delta = 0$ , nears the DFE of (2), as  $t \rightarrow \infty$  for  $R_0 \leq 1$ . This outcome revealed, given populace (where cases are most certainly to unsuccessfully finish treatment), with the supposition that the insignificant disease induced mortality ( $\delta = 0$ ), thus the DFE of (2) will be GAS on any occasion that  $R_0 \leq 1$ . Consequently, Onchocerciasis will be vacated from the populace without regard for the original sizes of the sub-populations on any occasion that  $R_0 \leq 1$ .

## 7. Global Stability (GAS) of an Endemic Steady State (EEP)

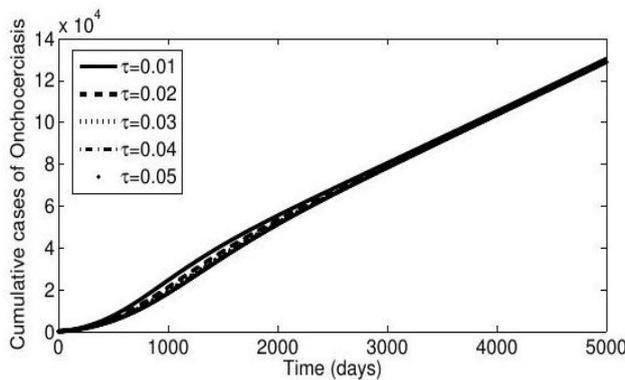
An exclusive case of (2) was examined in the absence of waning of medical intervention received by infected individuals (i.e. the malady bestows lifetime immunity), suggesting once treated, the persons remain cured for a lifetime ( $\sigma = 0$ ). Epidemiologically, the result gotten revealed that in a populace (where cases are most likely to unsuccessfully complete medical intervention), Human-Blackfly Onchocerciasis induced fatality and waning of medical intervention are insignificant (i.e.  $\delta = \sigma = 0$ ), the EEP will be GAS on any condition that  $R_0 > 1$  with the implication that Onchocerciasis will subsist in the population without taking into account the original sizes of the sub-population any condition that  $R_0 > 1$ .

## 3. RESULT AND DISCUSSION

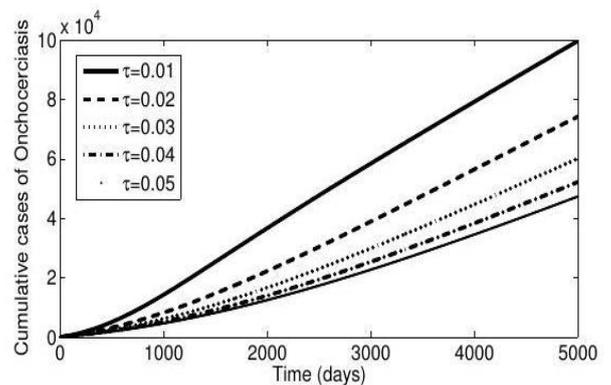
In this section, we examine the effect of definite critical parameters corresponding to unsuccessful completion of medical intervention on the kinetics of onchocerciasis. We numerically quantify the impact of failure to complete treatment regimen on the transmission dynamics of Human-Blackfly Onchocerciasis. Table 3 provides us with specific parameter values employed in the numerical evaluations. Parameters, both demographic cum epidemiological and Nigeria-specific, are employed in the numerical evaluations done herein. The overall population of Nigeria, in 2015, was calculated to be 184,635,279 (Countrymeter, 2016) thus  $\Lambda_H/\mu_H = 184,635,279$  in the absence of infection. The mean natural death rate per annum was calculated to be  $\mu_H = 0.02041$  or  $\mu_H = 0.000056 \text{ day}^{-1}$  (Countrymeter, 2016). Humans with the disease under consideration is calculated to be 17,800 in number having a corresponding 9.87% Onchocerciasis prevalence. The overall simulation (cum the associated plots) carried out herein were done employing MATLAB R2012a.

**Table 3: Baseline values for the parameters of the system (2)**

Parameter	Baseline values	Sample Range	References
$\mu_h$	$0.000056day^{-1}$	(0.00005,0.00006)	Countrymeter (2016)
$\Lambda_H$	$25day^{-1}$	(0.0000819,0.001085)	Estimated
$\alpha_H$	$0.00139day^{-1}$	(0.00137,0.00365)	Lakwo et al. (2020)
$\beta_H$	$0.0935day^{-1}$	(0,1)	Omondi et. al. (2017)
$\beta_V$	$0.0825day^{-1}$	(0,1)	Omondi et. al. (2017)
$\tau$	$0.0056day^{-1}$	(0,1)	Turner et al. (2015)
$\eta$	0.5	(0,1)	Variable
$\gamma$	$0.0003day^{-1}$	(0,0.01)	Assumed
$\sigma$	$0.0002 day^{-1}$	(0,0.001)	Assumed
$p$	0.5	(0,1)	Variable
$\delta$	0.000005	(0,0.000006)	Assumed
$\alpha_V$	$0.078 day^{-1}$	(0.0714,0.1667)	Hopkins and Boatin (2011)
$\mu_V$	$0.068 day^{-1}$	(0.0118,0.0714)	Hopkins and Boatin (2011)
$\Lambda_V$	$1000 day^{-1}$	(500 – 10000)	Hopkins and Boatin (2011)



(a)  $p = 0.2$

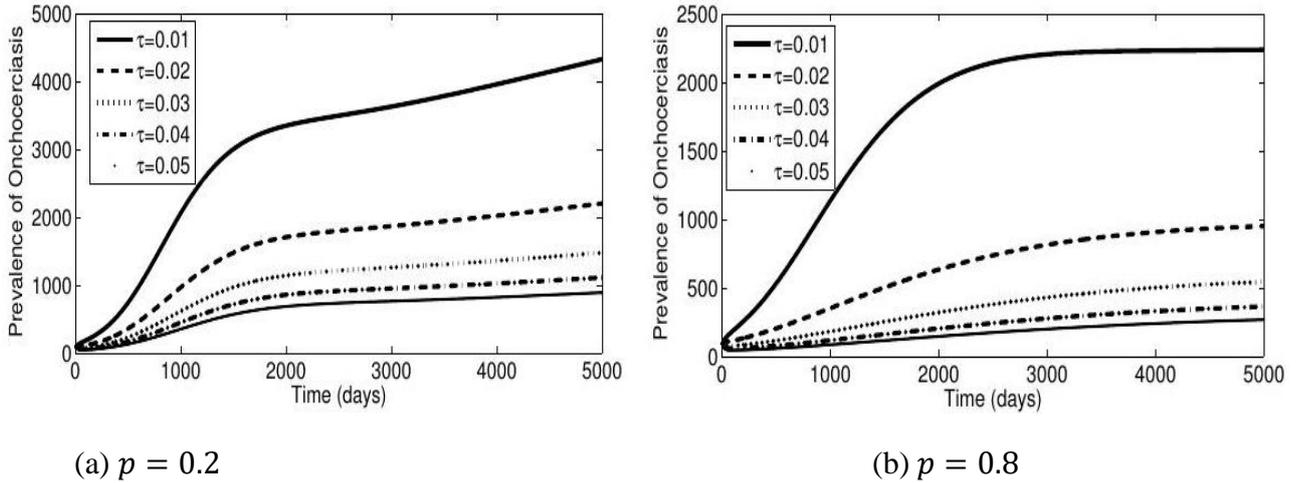


(b)  $p = 0.8$

**Figure 3:** Figure showing cumulative cases of onchocerciasis with varying values of  $\tau$ .

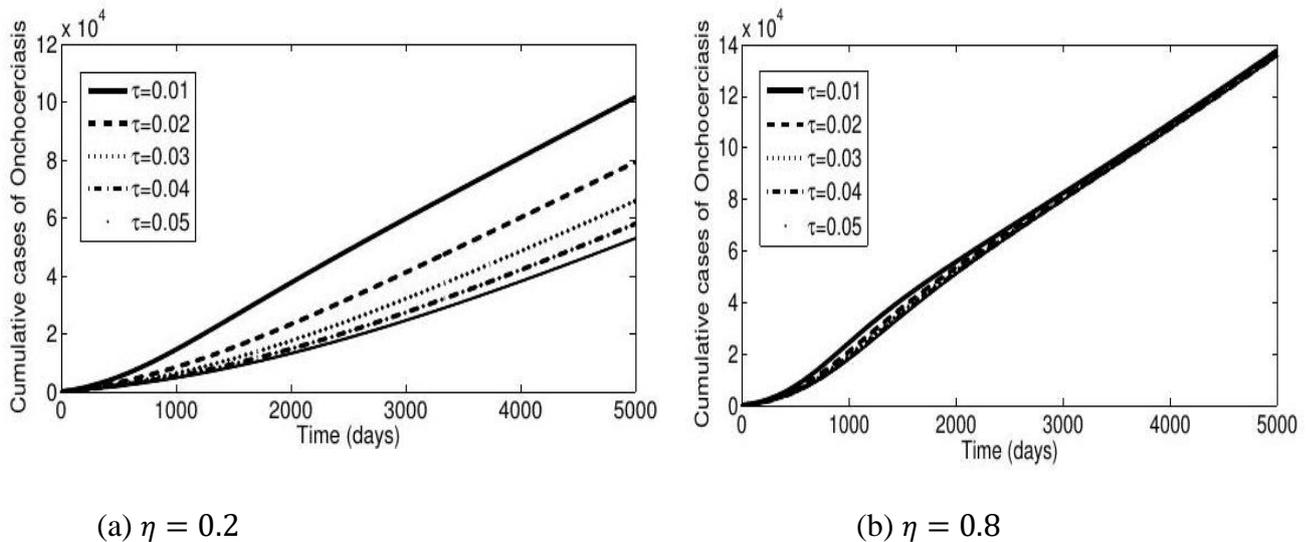
The fraction of cases who successfully exhausted their medical intervention ( $p$ ) plays an important role on the kinetics of the infection as seen in Figure 3. It is obvious, as revealed in Figure 3(a), that elevation in the treatment rate ( $\tau$ ) has marginal impact when only 20% of infected humans complete their treatment.

However, when 80% of infected humans complete their treatment, we see a more significant contraction in the cumulative cases with increase in the treatment rate (Figure 3(b)). We therefore see that the contraction in disease burden as a consequence of elevation in the medical intervention rate is significantly undermined when more infected humans do not complete their treatment regimen.



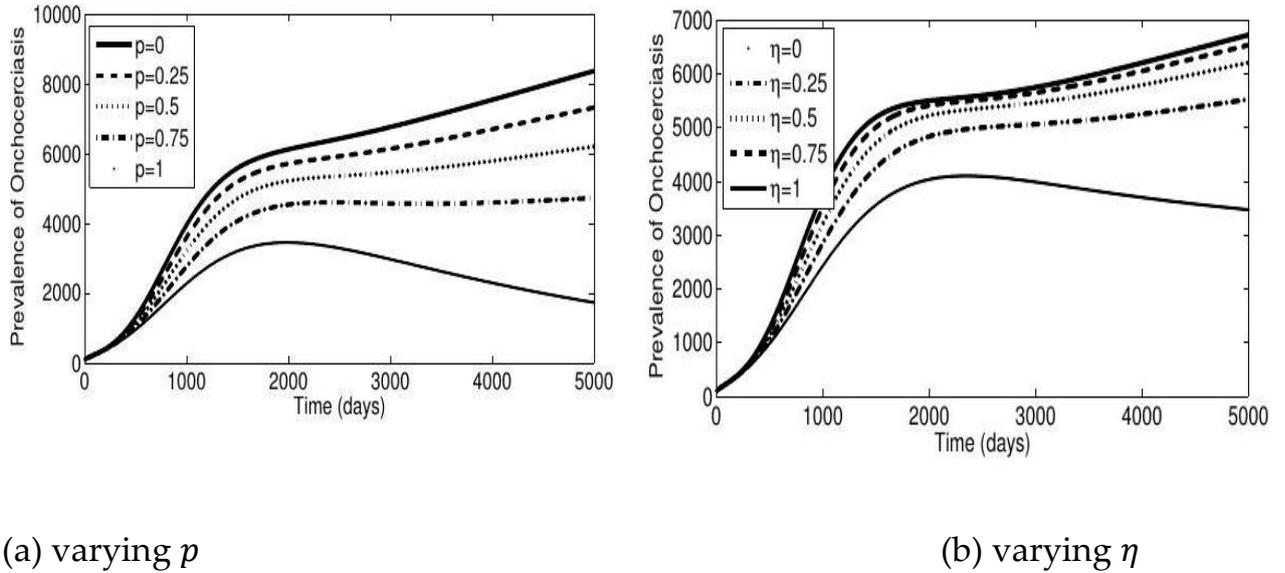
**Figure 4:** Figure showing prevalence of onchocerciasis with varying values of  $\tau$

This result in the Figures 4(a) and 4(b) showed that with only 20% of infected persons completing their treatment, a higher prevalence is recorded (see Figure 4(a)) as compared to when about 80% of infected persons completing their treatment (see Figure 4(b)). We therefore see that the contraction in disease burden as a consequence of elevation in the medical intervention rate is significantly undermined when more infected humans do not complete their treatment regimen.



**Figure 5:** Figure showing cumulative cases of onchocerciasis with changing values of  $\tau$ .





**Figure 7:** Figure showing prevalence of onchocerciasis with varying values of (a)  $p$  and (b)  $\eta$

Figure 7 showed the effect of the fraction of cases who successfully exhausted their medical intervention ( $p$ ) and the proportionate transference of humans who unsuccessfully complete their standard medical intervention ( $\eta$ ). We see that  $p$  has a more important effect on onchocerciasis prevalence (Figure 7(a)) as it results in less prevalence than  $\eta$  (Figure 7(b)). This means that putting more effort in making sure that the treatment regimen is completed for the required number of years will yield positive result in the control of onchocerciasis.

#### 4. CONCLUSION

Numerical examination of model (2) unravels the fact that the fraction of humans who successfully exhaust their standard medical intervention *paripasu* the proportionate transference of humans who unsuccessfully completed their standard medical intervention have important effect on the transmission dynamics of onchocerciasis in a population. Emphasis should not just be placed on mass drug administration only but also monitoring and making sure that individuals go through the complete treatment regimen for the required number of years. This finding is in line with the results reported by Tekle *et al.* (2012). Tekle *et al.* (2012) assessed the effect of long-term standard medical intervention of onchocerciasis with ivermectin in northern Nigeria, specifically in Kaduna State. Before standard medical intervention, the neighbourhood prevalence of skin-resident *O. volvulus* microfilaria expanse from 23.1% - 84.9%, with a central preponderance of 52.0%. After 15 years - 17 years of standard medical intervention, the prevalence had dropped to zero percent (i.e., 0%) in every

community observed and every one of the 3,703 medically tested persons returned a skin-snip negative result. However, it was also reported that standard medical intervention coverage of 77% (expanse 63-86%) of the overall population and approximately 92% of the eligible community was achieved (Tekle *et al.*, 2012). This very high treatment coverage may be one of the reasons why eradication was possible. Reports from Lakwo *et al.* (2020) stated that one of the reasons why onchocerciasis has not been eliminated in some countries and yet elimination has been achieved in certain others like the central and southern American countries may be due to conflict and civil unrest especially in African countries (Lakwo, *et al.*, 2020). This has affected geographical and therapeutic coverage of mass drug administration strategy (which is the primary tool deployed in war against onchocerciasis) (Tekle *et al.*, 2012). On the African continent, when the emphasis was shifted from onchocerciasis regulation to annihilation, the standard medical intervention coverage was changed from  $\geq 65\%$  to  $\geq 85\%$  and the geographical coverage to 100% (Lakwo, *et al.*, 2020). Such high coverage level will thus be very difficult to achieve in a population with civil unrest as the treatment will be disrupted from time to time and thus making it difficult for some person to complete their treatment regimen.

This work has therefore shown the important role played by treatment failure in the transmission dynamics of onchocerciasis. Thus, for control and possible elimination of onchocerciasis to be achieved, emphasis should not just be placed on mass drug administration (MDA) but also on the fraction (coverage) of confirmed cases who successfully complete their standard medical intervention.

## CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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