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Research article

Sensitivity analysis and parameters estimation for the transmission of lymphatic filariasis

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ABSTRACT

Lymphatic filariasis is a neglected tropical disease which poses public health concern and socio-economic challenges in developing and low-income countries. In this paper, we formulate a deterministic mathematical model for transmission dynamics of lymphatic filariasis to generate data by white noise and use least square method to estimate parameter values. The validity of estimated parameter values is tested by Gaussian distribution method. The residuals of model outputs are normally distributed and hence can be used to study the dynamics of Lymphatic filariasis. After deriving the basic reproduction number, $\mathcal{R}_0$ by the next generation matrix approach, the Partial Rank Correlation Coefficient is employed to explore which parameters significantly affect and most influential to the model outputs. The analysis for equilibrium states shows that the Lymphatic free equilibrium is globally asymptotically stable when the basic reproduction number is less a unity and endemic equilibrium is globally asymptotically stable when $\mathcal{R}_0 \geq 1$. The findings reveal that rate of human infection, recruitment rate of mosquitoes increase the average new infections for Lymphatic filariasis. Moreover, asymptomatic individuals contribute significantly in the transmission of Lymphatic filariasis.

1. Introduction

Lymphatic filariasis is a chronic parasitic mosquito-borne disease. It is considered as the most prevalent neglected tropical disease [1,2]. The disease is endemic and causes major public health and socio-economic challenges in tropical and sub-tropical regions especially in developing countries [3–5]. The World Health Organization (WHO) estimated that 863 million people from 73 countries are threatened by lymphatic filariasis and require Mass Drug Administration (MDA) intervention [6]. Lymphatic filariasis is caused by roundworms of the nematode family namely; *Brugia malayi*, *Brugia timori* and *Wuchereria bancrofti*, where *Wuchereria bancrofti* is responsible for at least 90% of total infections [7]. The disease cause impairments to human lymphatic system leading to enlargement and disfigurement of body parts. Consequently, this results into lymphoedema, elephantiasis and hydrocele. The impairments are accompanied by severe pain, permanent disability, defect in reproductive system, adenolymphangitis, damage of the kidney, social stigma and rarely death in chronic-infected individuals [8–10].

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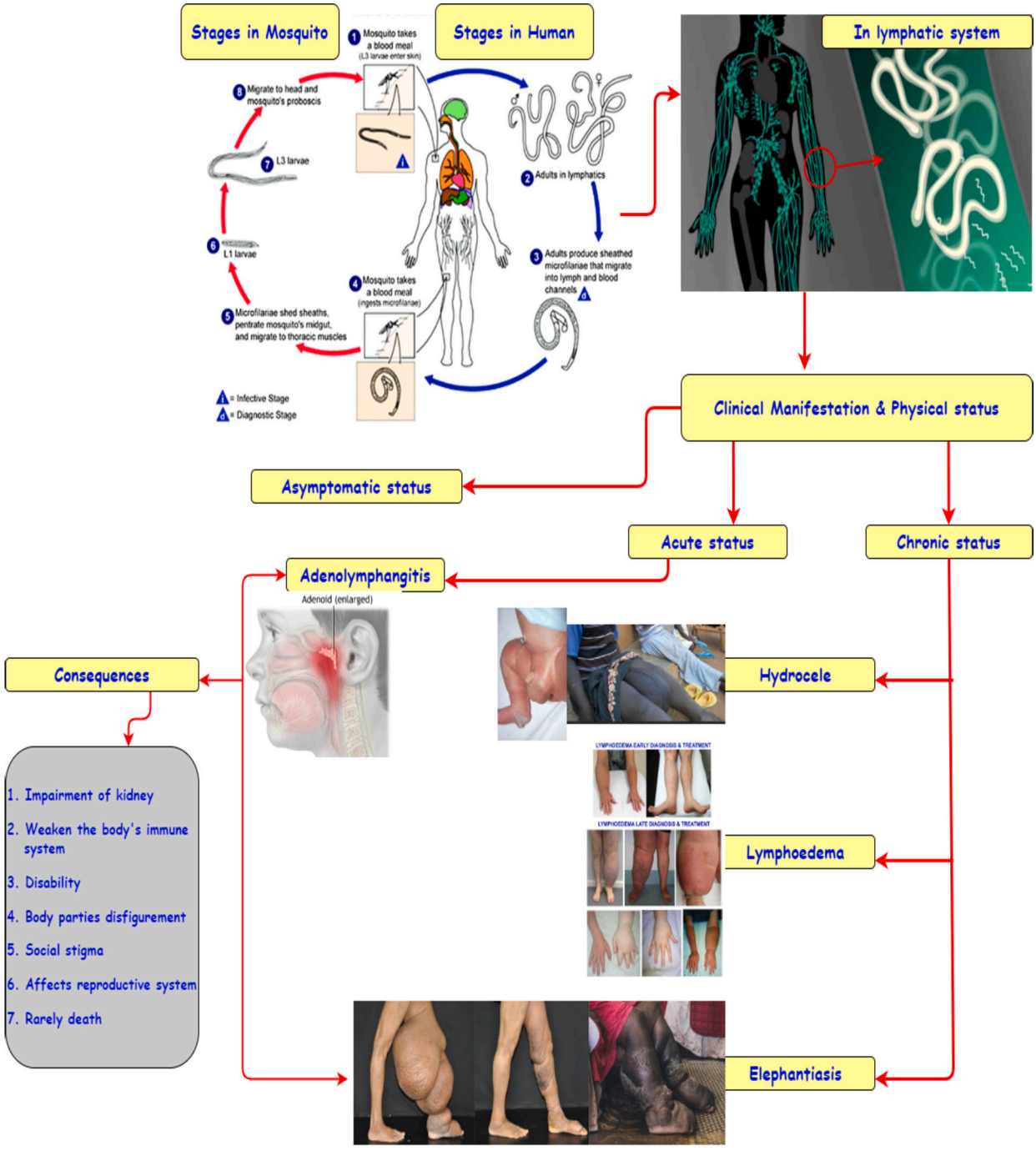


Fig. 1. The life cycle of microfilarie parasites, physical manifestations and consequences associated.

In humans, lymphatic filariasis is characterized by three phases namely asymptomatic, acute, and chronic. The stages can be manifested based on the body's distinctive immune attributes. In an asymptomatic condition, for instance, there is no noticeable symptoms while microfilariae parasites cause damage to the body's immune and lymphatic systems [9]. The Acute stage is associated with adenolymphangitis, local inflammation of lymph nodes and vessels, skins that leads to secondary bacterial infections due to partial loss of normal defense of lymphatic system [9,6]. When the disease develops into chronic stage, it results into hydrocele, lymphoedema, sub-optimal mental health, elephantiasis and social stigma due to body's part disfigurements. Therefore, lymphatic filariasis contribute considerably to loss income-earning opportunities, permanent disabilities, socio-economical burdens which include medical expenses and individual dependence as described in Fig. 1. Human being is a primary and definitive host of

microfilarie parasites while mosquito is an intermediate host [11]. The life time of parasites in the human body is approximated to be between $5-8$ years [12].

Mosquitoes as intermediate host transmit microfilariae parasites from an infected human to a susceptible human through blood-feeding [13]. In the intermediate host, microfilariae develop into infective larvae which can be transmitted to susceptible human [6]. Lymphatic filariasis is globally distributed with mosquitoes that are responsible for the transmission of the parasites differing geographically. For instance, in Africa, America, Asia and Pacific, lymphatic filariasis is transmitted by anopheles, culex, mansonia and aedes respectively [9].

To intervene the transmission, WHO recommends implementation of Mass Drug Administration (MDA) in countries at risks, to reduce lymphatic filariasis transmission and prevalence [6]. However, regardless of MDA treatment, the damage caused by lymphatic filariasis infection to lymphatic system is irreversible. While WHO ranks lymphatic filariasis as a second causative of long-term disability after leprosy, Centers for Disease Control and prevention (CDC) identifies it as the leading cause of permanent disability worldwide. It is estimated that one billion people are at risk of lymphatic filariasis infection and 120 million have been affected, 65% of those who are at risk of contracting lymphatic filariasis reside in the Southeast Asia, 30% in Africa, and the rest live in other parts of the tropical world [6]. In Tanzania specifically, Lymphatic Filariasis is endemic countrywide with high prevalence in the coastal regions such as Tanga, Pwani, Lindi, Mtwara and Dar es Salaam. In 2017, [14], conducted a survey which identified patients with lymphatic filariasis in Dar es salaam. The study reported a total of 6889 infected cases of which 60%, 32% and 8% had hydrocele, lymphoedema and lymphoedema-hydrocele co-infection respectively. The global response to lymphatic filariasis transmission and its associated burdens, include a Global Programme to Eliminate Lymphatic Filariasis GPELF which was launched by WHO in 2000 and new neglected tropical diseases road map from 2020 to 2030. Despite WHO 2000 & 2020 preventive chemotherapy measures to halt the spread of lymphatic filariasis infection, the disease is still endemic.

Mathematical modeling is an important and scientific tool for investigating and analyzing epidemiological dynamics of infectious diseases for designing appropriate control intervention programmes [15]. Regarding mathematical modeling for lymphatic filariasis, a number of deterministic and statistical models have been formulated and analyzed. These include [8,16–28] and [29]. Although asymptomatic individuals play a significant role in disease transmission, none of the aforementioned studies have considered the simultaneous inclusion of asymptomatic, acute, and chronically infected populations in their modeling approaches. This paper presents a deterministic model that generates data through random simulation with white noise, estimates parameter values, and investigates the dynamics of lymphatic filariasis in both humans and mosquitoes, taking into account all three categories of infected individuals. The objective of this study is to provide insights at the community level, enhancing awareness and improving the general understanding of transmission dynamics involving carriers and asymptomatic individuals. Furthermore, this research aims to make a substantial contribution to the existing literature and establish a new platform for future studies. The findings of this study will also be valuable for government officials and policymakers, aiding in the development of effective control strategies.

The paper is organized as follows: In Section 2, a deterministic mathematical model for the dynamics of lymphatic filariasis is formulated. Section 3 is devoted to model fitting and analysis. The implementation of numerical simulation is done in section 4. The discussion and conclusion is presented in Section 5.

2. Model development

The model for Lymphatic filariasis divides human populations into five classes namely susceptible $S(t)$, exposed $E(t)$, Asymptomatic $A(t)$, acute $I_1(t)$ and chronic $I_2(t)$ and the mosquitoes population into susceptible $S_M(t)$, exposed $E_M(t)$ and infected $I_M(t)$ classes. The susceptible humans, $S(t)$ are recruited at rate Π_H, and become exposed when they contract lymphatic filariasis through infectious mosquito bites $I_M(t)$ at rate β [1]. Exposed humans, $E(t)$ progress to asymptomatic class, $A(t)$ at a rate α. The asymptomatic stage causes damage of lymphatic system, kidneys and changes in the body immune system leading to progression to either acute stage at rate ξ or chronic stage at a rate ϕ. A proportion of exposed individual progresses to acute stage $I_1(t)$ and chronic stage $I_2(t)$ at rates ρ and ψ, respectively [6]. Moreover, individual in acute class progress to chronic class at a pace σ. Lymphatic filariasis induces mortality in chronic class at a rate δ. Human classes suffer natural death at a rate μ_h.

The susceptible mosquitoes $S_M(t)$ are recruited at a rate Π_M, and decline as they contract lymphatic filariasis through biting infected individuals in asymptomatic $A(t)$, acute $I_1(t)$ and chronic $I_2(t)$ classes and become exposed at a rate:

$$\lambda = \beta_2 A + \beta_3 I_1 + \beta_1 I_2, \tag{1}$$

from Eq. (1), β_1, β_2 and β_3 are rates at which susceptible mosquitoes acquire infection from individuals in chronic, asymptomatic and acute classes respectively.

The Lymphatic filariasis model development follows the following assumptions: there is no vertical transmission for lymphatic filariasis in humans; migration is not considered; the rate of infection is assumed to be density dependent [30,19], also known as principle of mass action; the parasites that cause lymphatic filariasis are transmitted only by a mosquito vector; infected humans can not recover from infection; chronic infected individuals suffer disease induced mortality. Fig. 2 illustrates the model flowchart.

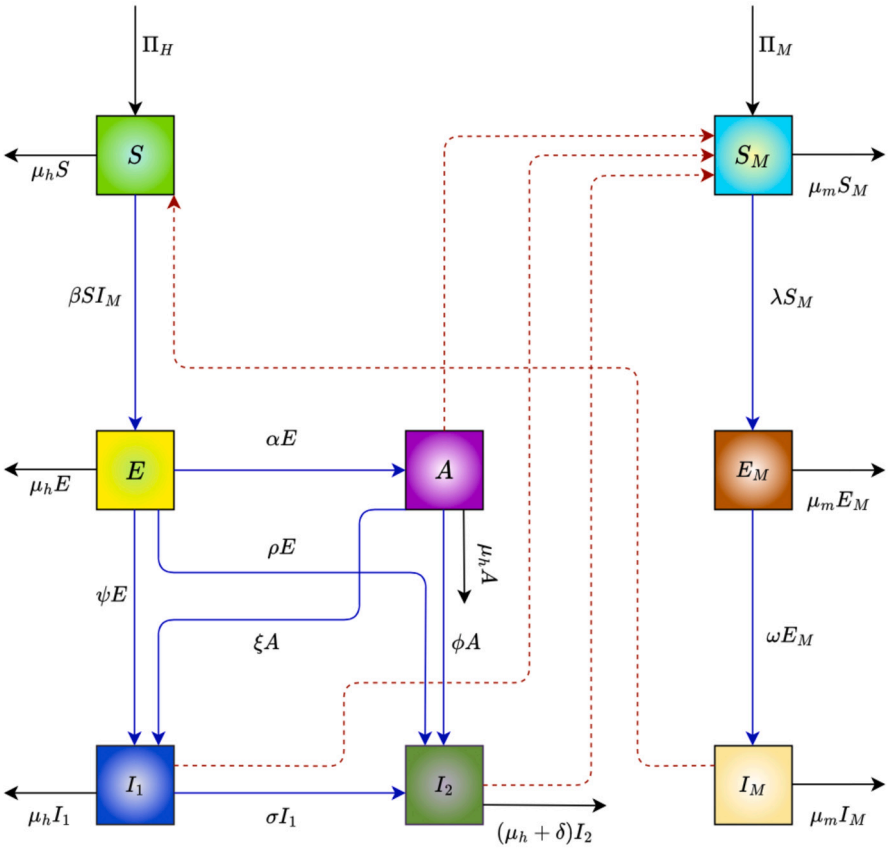


Fig. 2. Compartmental model for the transmission of lymphatic filariasis in humans and mosquito vectors.

The transmission dynamics of lymphatic filariasis is described by non-linear system of ordinary differential equations:

$$\begin{cases} \frac{dS(t)}{dt} = \Pi_H - \beta I_M S - \mu_h S, \\ \frac{dE(t)}{dt} = \beta I_M S - (\alpha + \rho + \psi + \mu_h) E, \\ \frac{dA(t)}{dt} = \alpha E - (\xi + \phi + \mu_h) A, \\ \frac{dI_1(t)}{dt} = \psi E + \xi A - (\sigma + \mu_h) I_1, \\ \frac{dI_2(t)}{dt} = \rho E + \phi A + \sigma I_1 - (\delta + \mu_h) I_2, \\ \frac{dS_M(t)}{dt} = \Pi_M - \lambda S_M - \mu_m S_M \\ \frac{dE_M(t)}{dt} = \lambda S_M - (\omega + \mu_m) E_M \\ \frac{dI_M(t)}{dt} = \omega E_M - \mu_m I_M \end{cases} \tag{2}$$

with the following initial conditions:

$$S(0) > 0; E(0) \geq 0; A(0) \geq 0; I_1(0) \geq 0; I_2(0) \geq 0; S_M(0) > 0; E_M(0) \geq 0; \text{ and } I_M(0) \geq 0.$$

3. Model analysis

3.1. Positivity and boundedness of solutions

The model system (2) is tested to determine whether it is mathematically well-posed and biologically feasible in region $\Gamma = \{(S, E, A, I_1, I_2, S_M, E_M, I_M) \in \mathbb{R}^8_+\}$. If the model solutions are bounded and non-negative, then such a model is said to be well posed and biologically meaningful.

Theorem 1. *Let* $S(0) > 0;\ E(0) \geq 0;\ A(0) \geq 0;\ I_1(0) \geq 0;\ I_2(0) \geq 0;\ S_M(0) > 0;\ E_M(0) \geq 0;$ *and* $I_M(0) \geq 0$ *be non-negative initial conditions, then the solutions* $(S, E, A, I_1, I_2, S_M, E_M, I_M)$ *of model* (2) *will remain positive for all time* $t \geq 0$.

To show that the model solutions are positive for all $t \geq 0$, let $t_1 = sup\{t > 0 :\ S > 0,\ E > 0,\ A > 0,\ I_1 > 0,\ I_2 > 0,\ S_M > 0,\ E_M > 0,\ I_M > 0\}$. The first equation for susceptible humans in model system (2) can be written as;

$$\frac{dS}{dt} = \Pi_H - (\beta I_M + \mu_h)S \geq -(\beta I_M + \mu_h)S.$$

Separation of variables yields;

$$\frac{dS}{S} \geq -(\beta I_M + \mu_h)dt.$$

Integration and application of initial condition gives

$$S(t) \geq S(0)e^{-\int_0^{t_1} (\beta I_M(\tau) + \mu_h)d\tau} \geq 0. \tag{3}$$

Using similar approach used to obtain Eq. (3) for the rest of equations it can be shown that all solutions of the model system (2) are positive for all $t \geq 0$.

To establish boundedness of the model solutions, we consider the total human and mosquitoes populations respectively to obtain:

$$\begin{aligned} \frac{dN_H}{dt} &\leq \Pi_H - \mu_H N_H, \\ \frac{dN_M}{dt} &\leq \Pi_M - \mu_m N_M. \end{aligned} \tag{4}$$

The solution of human equation in Eq. (4) is:

$$N_H(t) \leq \frac{\Pi_H}{\mu_h} + \left(N_H(0) - \frac{\Pi_H}{\mu_h}\right) e^{-\mu_h t} \tag{5}$$

Applying standard comparison theorem on Eq. (5) as used in [31], when $N_H(0) > \frac{\Pi_H}{\mu_h}$ and $N_H(0) < \frac{\Pi_H}{\mu_h}$ we obtain;

$$\begin{aligned} &\frac{\Pi_H}{\mu_h} \leq N_H(t) \leq \frac{\Pi_H}{\mu_h} + \left(N_H(0) - \frac{\pi_H}{\mu_h}\right) e^{-\mu_h t}, \text{and} \\ &\frac{\Pi_H}{\mu_h} + \left(N_H(0) - \frac{\Pi_H}{\mu_h}\right) e^{-\mu_h t} \leq N_H(t) \leq \frac{\Pi_H}{\mu_h}, \end{aligned} \tag{6}$$

respectively. As $t \to \infty$, Eq. (4) becomes;

$$0 \leq N_H(t) \leq \frac{\Pi_H}{\mu_h}. \tag{7}$$

Applying the same procedure for the mosquito equation in Eq. (7), we have:

$$0 \leq N_M(t) \leq \frac{\Pi_M}{\mu_m}. \tag{8}$$

Eq. (7) and Eq. (8) shows that all solutions of the model (2) are positively invariant in the region Γ. Therefore, lymphatic filariasis model is mathematically and epidemiologically well-posed in the region Γ.

3.2. Disease free equilibrium (DFE) and basic reproduction number $\mathcal{R}_0$

When lymphatic filariasis does not exist in human and mosquito vector populations, we obtain the lymphatic filariasis free equilibrium $\mathcal{E}_0$ as follows:

$$\mathcal{E}_0 = \left(\frac{\Pi_H}{\mu_h}, 0, 0, 0, 0, \frac{\Pi_M}{\mu_m}, 0, 0\right).$$

The basic reproduction number, $\mathcal{R}_0$ is the average number of secondary infections produced by a single infected individual in a completely susceptible population during one's infectious period [32,33]. Using the next generation matrix method, the basic reproduction number, $\mathcal{R}_0$ is given by:

$$\mathcal{R}_0 = \frac{1}{\mu_m}\sqrt{\frac{\omega\beta\Pi_H\Pi_M}{\mu_h}\left(\frac{\beta_1(\alpha(\xi\sigma+\phi\eta_3)+\eta_2(\sigma\psi+\rho\eta_3))+\eta_4(\beta_3(\alpha\xi+\phi\eta_2)+\alpha\beta_2\eta_3)}{\eta_1\eta_2\eta_3\eta_4\eta_5}\right)} \tag{9}$$

where

$$\eta_1=(\alpha+\rho+\psi+\mu_h),\ \eta_2=(\xi+\phi+\mu_h),\ \eta_3=(\sigma+\mu_h),\ \eta_4=(\delta+\mu_h),\ \eta_5=(\omega+\mu_m).$$

3.3. Global stability of DFE

The model behaviour at the disease free equilibrium point, $\mathcal{E}_0$ is investigated using Metzler matrix as applied by Castillo-Chavez et al. [34]. Let X_m denote non-transmitting class, X_n be transmitting class and X_{DFE} be Disease Free equilibrium. Whereby:

$$X_m=\begin{pmatrix} S \\ \\ S_M \end{pmatrix},\quad X_n=\begin{pmatrix} E \\ A \\ I_1 \\ I_2 \\ E_M \\ I_M \end{pmatrix},\ \text{and}\ \ X_m-X_{DFE}=\begin{pmatrix} S-\dfrac{\Pi_H}{\mu_h} \\ \\ S_M-\dfrac{\Pi_M}{\mu_m} \end{pmatrix}$$

The system that describes the present model can be written as:

$$\begin{cases} \dfrac{dX_m}{dt}=A(X_m-X_{DFE})+BX_n, \\ \dfrac{dX_n}{dt}=CX_n. \end{cases} \tag{10}$$

Matrices A, B and C are to be computed from Eq. (10). The lymphatic filariasis disease free equilibrium $\mathcal{E}_0$ is globally asymptotically stable if matrix A has negative eigenvalues and C is Metzler matrix [35]. Matrices A, B and C are given by:

$$A=\begin{pmatrix} -\mu_h & 0 \\ 0 & -\mu_m \end{pmatrix},\quad B=\begin{pmatrix} 0 & 0 & 0 & 0 & 0 & -\dfrac{\beta\Pi_H}{\mu_h} \\ 0 & -\dfrac{\beta_2\Pi_M}{\mu_m} & -\dfrac{\beta_3\Pi_M}{\mu_m} & -\dfrac{\beta_1\Pi_M}{\mu_m} & 0 & 0 \end{pmatrix},\ \text{and}$$

$$C=\begin{pmatrix} -(\alpha+\rho+\psi+\mu_h) & 0 & 0 & 0 & 0 & \dfrac{\beta\Pi_H}{\mu_h} \\ \alpha & -(\xi+\phi+\mu_h) & 0 & 0 & 0 & 0 \\ \psi & \xi & -(\sigma+\mu_h) & 0 & 0 & 0 \\ \rho & \phi & \sigma & -(\delta+\mu_m) & 0 & 0 \\ 0 & \dfrac{\beta_2\Pi_M}{\mu_m} & \dfrac{\beta_3\Pi_M}{\mu_m} & \dfrac{\beta_1\Pi_M}{\mu_m} & -(\omega+\mu_m) & 0 \\ 0 & 0 & 0 & 0 & \omega & -\mu_m \end{pmatrix}$$

Since the eigenvalues of the matrix A are negative and the off-diagonal elements of the matrix C are non-negative then the lymphatic filariasis free equilibrium $\mathcal{E}_0$ is globally asymptotically stable.

Theorem 2. *The disease free equilibrium $\mathcal{E}_0$ is globally asymptotically stable when $\mathcal{R}_0<1$ and unstable otherwise.*

3.4. Existence of disease endemic equilibrium

In the presence of lymphatic filariasis, there exists non-trivial solutions which is commonly known as endemic equilibrium point. By setting all equations to zero in Eq. (2) as follows:

$$\begin{cases} 0 = \Pi_H - \beta I_M^* S^* - \mu_h S^*, \\ 0 = \beta I_M^* S^* - (\alpha + \rho + \psi + \mu_h) E^*, \\ 0 = \alpha E^* - (\xi + \phi + \mu_h) A^*, \\ 0 = \psi E^* + \xi A^* - (\sigma + \mu_h) I_1^*, \\ 0 = \rho E^* + \phi A^* + \sigma I_1^* - (\delta + \mu_h) I_2^*, \\ 0 = \Pi_M - \lambda S_M^* - \mu_m S_M^* \\ 0 = \lambda S_M^* - (\omega + \mu_m) E_M^* \\ 0 = \omega E_M^* - \mu_m I_M^* \end{cases} \tag{11}$$

By writing all equations in Eq. (11) in terms of I_M^* and computing its value gives:

$$I_M^* = \frac{\omega \Pi_M \mu_h \left(\frac{\omega\beta\Pi_H\Pi_M}{\mu_m^2\mu_h} \left(\frac{\beta_1(\alpha(\xi\sigma+\phi\eta_3)+\eta_2(\sigma\psi+\rho\eta_3))+\eta_4(\beta_3(\alpha\xi+\phi\eta_2)+\alpha\beta_2\eta_3)}{\eta_1\eta_2\eta_3\eta_4\eta_5} \right) - 1 \right)}{\frac{\eta_5\mu_h\omega\beta\Pi_H\Pi_M}{\mu_m^2\mu_h} \left(\frac{\beta_1(\alpha(\xi\sigma+\phi\eta_3)+\eta_2(\sigma\psi+\rho\eta_3))+\eta_4(\beta_3(\alpha\xi+\phi\eta_2)+\alpha\beta_2\eta_3)}{\eta_1\eta_2\eta_3\eta_4\eta_5} \right) + \beta\omega\Pi_M} \tag{12}$$

Simplifying Eq. (12) and use Eq. (9), we have

$$\mathcal{R}_0^2 = \frac{\omega\beta\Pi_H\Pi_M}{\mu_m^2\mu_h} \left(\frac{\beta_1(\alpha(\xi\sigma+\phi\eta_3)+\eta_2(\sigma\psi+\rho\eta_3))+\eta_4(\beta_3(\alpha\xi+\phi\eta_2)+\alpha\beta_2\eta_3)}{\eta_1\eta_2\eta_3\eta_4\eta_5} \right)$$

Substituting into equation (12), we have $I_M^* = \dfrac{\omega\Pi_M\mu_h(\mathcal{R}_0^2-1)}{\eta_5\mu_h\mathcal{R}_0^2 + \beta\omega\Pi_M}$.

Direct back substitution yields endemic equilibrium point $\mathcal{E}^* = (S^*, E^*, A^*, I_1^*, I_2^*, S_M^*, E_M^*, I_M^*) \in \mathbb{R}_+^8$, where:

$$S^* = \frac{\eta_5\mu_h\mu_m\Pi_H\mathcal{R}_0^2 + \beta\omega\Pi_H\Pi_M}{\mu_h(\beta\omega\Pi_M + \eta_5\mu_m\mu_h)\mathcal{R}_0^2}, \quad E^* = \frac{\beta\omega\mu_h\Pi_H\Pi_M(\mathcal{R}_0^2-1)}{\eta_1\mu_h(\beta\omega\Pi_M + \eta_5\mu_m\mu_h)\mathcal{R}_0^2},$$

$$A^* = \frac{\alpha\omega\mu_h\beta\Pi_M\Pi_H(\mathcal{R}_0^2-1)}{\eta_1\eta_2\mu_h(\beta\omega\Pi_M + \eta_5\mu_m\mu_h)\mathcal{R}_0^2}, \quad I_1^* = \frac{(\psi\eta_2+\xi\alpha)\beta\omega\mu_h\Pi_M\Pi_H(\mathcal{R}_0^2-1)}{\eta_1\eta_2\eta_3\mu_h(\beta\omega\Pi_M + \eta_5\mu_m\mu_h)\mathcal{R}_0^2},$$

$$I_2^* = \frac{(\eta_3(\rho\eta_2+\alpha\phi)+\sigma(\psi\eta_2+\xi\alpha))\beta\omega\mu_h\Pi_H\Pi_M(\mathcal{R}_0^2-1)}{\eta_1\eta_2\eta_3\eta_4\mu_h(\beta\omega\Pi_M + \eta_5\mu_m\mu_h)\mathcal{R}_0^2}, \quad S_M^* = \frac{\Pi_M}{\Omega+\mu_m},$$

$$E_M^* = \frac{\Omega\Pi_M}{\eta_5(\Omega+\mu_m)}, \quad I_M^* = \frac{\omega\Pi_M\mu_h(\mathcal{R}_0^2-1)}{\eta_5\mu_h\mathcal{R}_0^2 + \beta\omega\Pi_M},$$

whereby;

$$\Omega = \frac{\left(\beta_2\alpha\eta_3\eta_4 + \beta_1(\eta_3(\rho\eta_2+\alpha\phi)+\sigma(\psi\eta_2+\xi\alpha)) + \beta_3(\psi\eta_2+\xi\alpha)\right)\beta\omega\mu_h\Pi_H\Pi_M(\mathcal{R}_0^2-1)}{\eta_1\eta_2\eta_3\eta_4\mu_h(\beta\omega\Pi_M + \eta_5\mu_m\mu_h)\mathcal{R}_0^2}$$

Since each variable of $\mathcal{E}^*$ depends on the basic reproduction number $\mathcal{R}_0$, therefore lymphatic filariasis persists when the basic reproduction number $\mathcal{R}_0 \geq 1$ as summarized in Theorem 3

Theorem 3. *The model system (2) has a unique endemic equilibrium $\mathcal{E}^*$ whenever $\mathcal{R}_0 \geq 1$.*

3.5. Global sensitivity analysis

It is overtly true that obtaining accuracy results in mathematical models is difficult due to uncertainties in input or experimental data used to approximate parameter values. In this section, A Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC) are used in uncertainty analysis to explore all parameters in a model space. The PRCC is a robust sensitivity measure for non-linear systems which are monotonic in relationship between input and output by using scatter plots. The scatter plots enhance graphic detection of non-monotonicities, correlations and non-linearities between the inputs and outputs of the model [36]. We implement LHS algorithm for uniform and normal probability density functions which is efficient and reliable for nonlinear ordinary differential equations [37,38]. The PRCC is used to measure the strength of linear association between model inputs and outputs and provide PRCC-indices as used in Manno et al. [39]. If θ_i represents input parameters and Y_i represents model outputs, then the PRCC index r_{θ_i,Y_i} is given by:

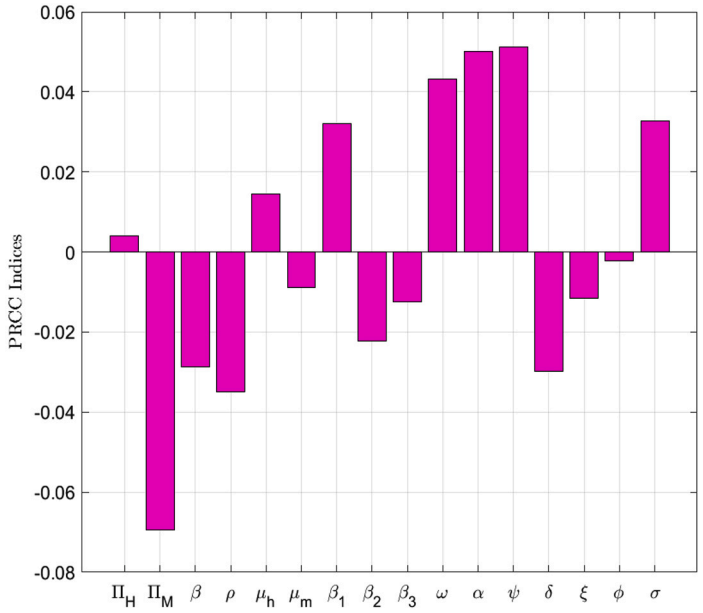


Fig. 3. Plots of regression coefficient for outputs measure against regression coefficients for input parameters: Sampling-based correlation indexes computed on LHS algorithm.

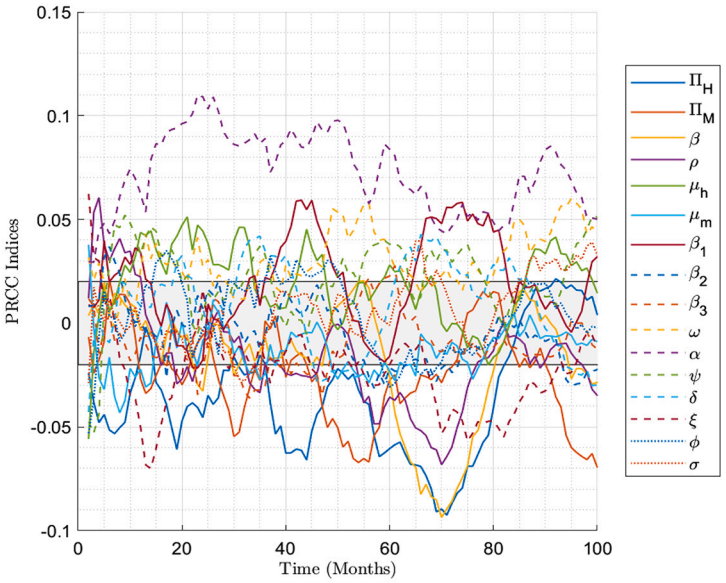


Fig. 4. PRCCs over time of the eight-compartmental model uncertainty and sensitivity analysis. The PRCC values ranging between −0.02 to 0.02 are statistically insignificant regardless the sensitivity of parameter changes as the dynamic system progress.

$$r_{\theta_i,Y_i} = \frac{\mathrm{Cov}(\theta_i, Y_i)}{\sqrt{\mathrm{Var}(\theta_i)\mathrm{Var}(Y_i)}} = \frac{\sum_{i=1}^{n}(\theta_i - \bar{\theta})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^{n}(\theta_i - \bar{\theta})^2 \sum_{i=1}^{n}(Y_i - \bar{Y})^2}} \tag{13}$$

The PRCC results reveal the contribution of each parameter and corresponding uncertainty to the model. The parameters whose PRCC values are closer or equal to zero are statistically insignificant. Fig. 3 indicates that β_1, α ω, σ and ψ have strong correlation to model outputs Y_i based on their PRCC values which are computed using Eq. (13). However, Π_M, β, ρ and δ have inversely proportional relationship to model outputs. Fig. 4 shows the sensitivity of PRCC values over entire time interval of model simulation which access the significance and indicate how the sensitivity of each parameter vary the dynamics of the model system. This suggests that, to control lymphatic filariasis in humans, more efforts should be directed to reduce the rate of infections by intervening the transmission and control the mosquito-vectors.

Table 1
Parameter Values Month^{-1}.

Parameter	Baseline	Reference	Range	Estimates	Normal(Mean(μ), std(σ))
Π_H	20.0000	Assumed	[10.0000 30.0000]	22	$\mathcal{N}(20.0000,\ 2.2048)$
β	0.0005	[26]	[0.00010 0.0050]	0.00054	$\mathcal{N}(0.0005,\ 6.2\times10^{-4})$
β_1	0.0015	Assumed	[0.0010 0.0030]	0.00183	$\mathcal{N}(0.0015,\ 6.6\times10^{-4})$
β_2	0.0035	Assumed	[0.0015 0.0045]	0.00386	$\mathcal{N}(0.0035,\ 7.9\times10^{-4})$
β_3	0.00025	[29]	[0.00015 0.00035]	0.000246	$\mathcal{N}(0.00025,\ 5.0\times10^{-4})$
ρ	0.00032	[20]	[0.00025 0.0075]	0.00033	$\mathcal{N}(0.00032,\ 1.0\times10^{-3})$
ψ	0.0015	Assumed	[0.0025 0.0085]	0.001521	$\mathcal{N}(0.0015,\ 3.3\times10^{-4})$
δ	0.000015	[29]	[0.00001 0.00003]	0.000021	$\mathcal{N}(0.000015,\ 3.7\times10^{-4})$
ω	0.0055	[16]	[0.0035 0.0065]	0.00537	$\mathcal{N}(0.0055,\ 3.32\times10^{-4}$
ϕ	0.00045	Assumed	[0.0003 0.0009]	0.000395	$\mathcal{N}(0.00045,\ 5.0\times10^{-4})$
Π_M	100000	[22]	[50000 150000]	116300	$\mathcal{N}(100000,\ 598.96)$
μ_h	0.0142	[41,22]	[0.0100 0.0200]	0.01391	$\mathcal{N}(0.0142,\ 1.0\times10^{-4})$
α	0.0200	[29]	[0.0100 0.0500]	0.03526	$\mathcal{N}(0.02,\ 5\times10^{-3})$
μ_m	0.050000	[18]	[0.0100 1.5000]	0.08521	$\mathcal{N}(0.05000,\ 0.0062)$
ξ	0.00030	Assumed	[0.0025 0.0055]	0.00043	$\mathcal{N}(0.00030,\ 7.905\times10^{-4})$
σ	0.0012	Assumed	[0.0010 0.0030]	0.001209	$\mathcal{N}(0.0012,\ 1.87\times10^{-4})$

3.6. Model fitting and parameters estimation

After formulating the model and checking whether its solutions are positive invariant, another important aspect is to determine how the model is a good representation of the real data. Lymphatic filariasis is one among neglected diseases, there is no sufficient data in records about it. In this section, we use a standard method non-linear least square method to generate data and use them to estimate the parameters. Let our model with true choice of parameter vector θ_0 in n observations be $Y_{i=1}^{n}$. However, this can be affected by random error of measurement, the model output is given by

$$Y_i = Z(t_i,\theta_0) + f(t_i,\theta_0), \tag{14}$$

where $Z(t_i,\theta_0)$ is the solution of the model when actual parameters are used and $f(t_i,\theta_0)$ is error due to measurement. To minimize the error, we use Eq. (14) to obtain sum of squares as $SSE(\theta)$ such that

$$SSE(\theta) = \sum_{i=1}^{n} \left(Y_i - f(t,\theta)\right)^2. \tag{15}$$

SSE(θ) in Eq. (15) defines the model simulation outputs and artificial generated data to mimic the real situation in absence of longtime dynamical data as implemented by [40]. The model is numerically simulated by employing the Euler's formula and the *fminsearch* function independently with initial guess of parameters in MATLAB R2018a. Moreover, the generated data are used to estimate parameters which are listed in Table 1. The validity of the estimated parameter values are tested by the nature of distribution of their residuals in all model outputs. Results show that they are reliable since they have normal distribution as depicted in Fig. 6. The model simulation is implemented subject to the following initial conditions: $E(0)=1,\ A(0)=1,\ I_1(0)=1,\ I_2(0)=1,\ S(0)=\Pi_H/\mu_h-(E(0)+A(0)+I_1(0)+I_2(0)),\ E_M(0)=1,\ I_M(0)=1,\ S_M(0)=\Pi_M/\mu_m-(E_M(0)+I_M(0))$.

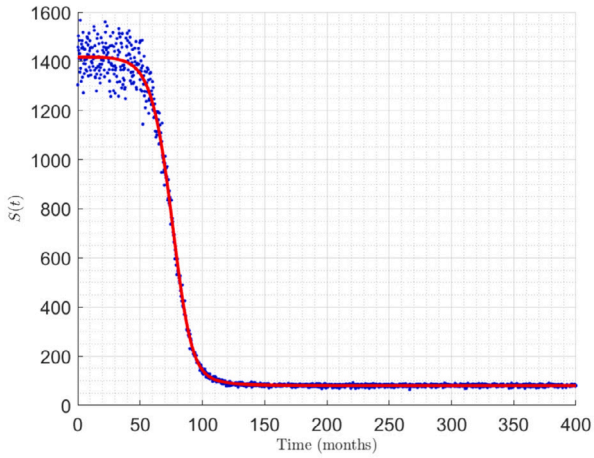
4. Numerical simulations

After estimating the parameter values, we now simulate the model to observe the long term behaviour of the dynamics of lymphatic filariasis. We begin with all classes and later concentrate on infected classes by considering sensitive parameters. The mathematical model (2) is simulated using parameter values in Table 1 to study the dynamics of lymphatic filariasis.

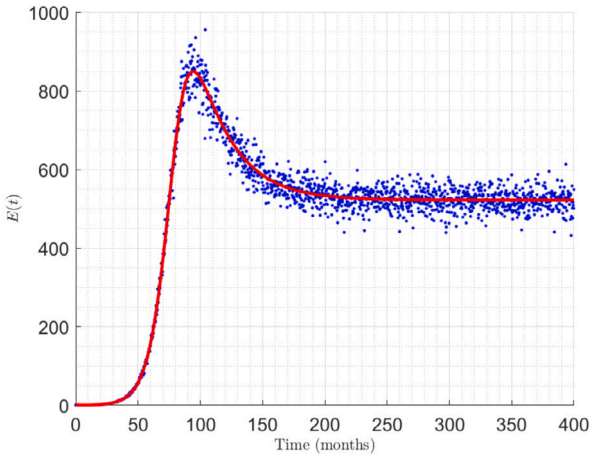
5. Discussion and conclusion

5.1. Discussion

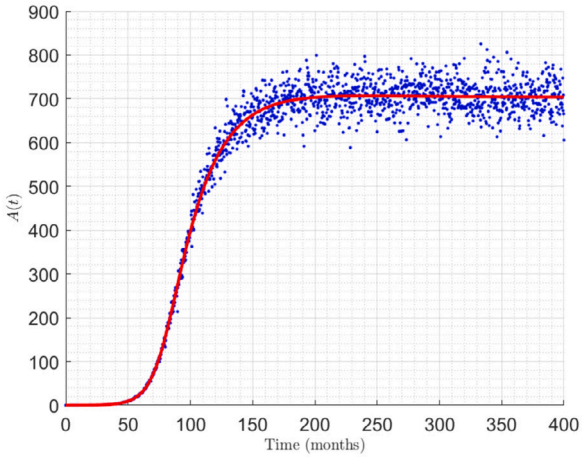
Fig. 8(a) indicates that the number of susceptible humans decrease with time following infection by lymphatic filariasis whereby the whole population stabilize after 100 months. On the other hand, susceptible mosquito population follow the similar trend, whereas only large number become infected after 100 months. Susceptible classes have inverse relationship with acute-infected, chronic-infected and asymptomatic classes as illustrated in Fig. 8 (b). Initially, exposed class for humans increase to maximum in the first 100 months, thereafter decrease to attain the steady state after 150 months. Asymptomatic, infected-acute and infected-chronic increases to their maximum, then attain their equilibrium states. Consequently, exposed and infected classes for mosquito population follow similar trend. Simulation indicates that asymptomatic class contribute significantly in transmission and has large number of human population compared to infected-acute and chronic. Numerical data and scatter plots for generated data follow the similar trend when are plotted concurrently as shown in Fig. 5 and 6. The result reveals residual in all outputs are normally distributed showing that the proposed model fitting and parameter values are stable, effective and reliable for future applications as depicted in



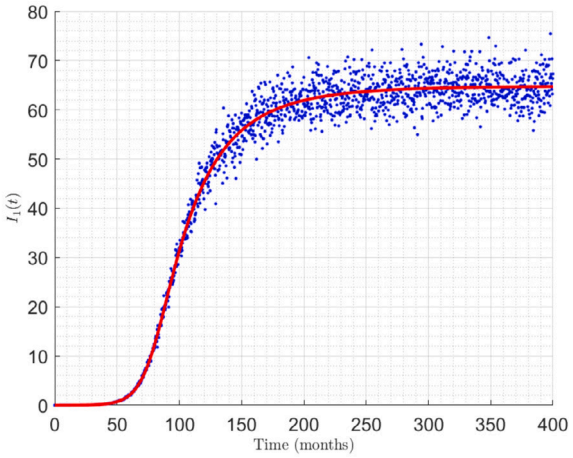
Susceptible human population



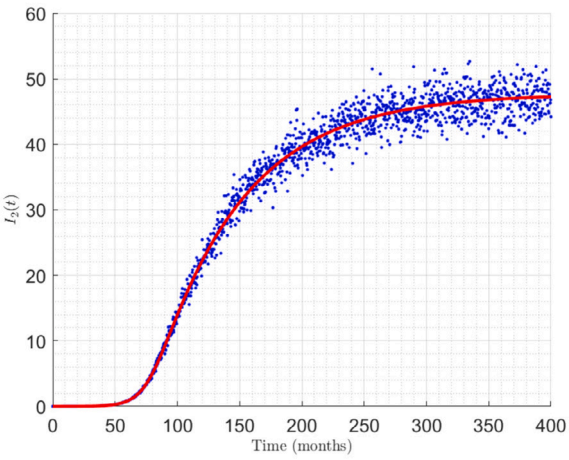
Exposed human population



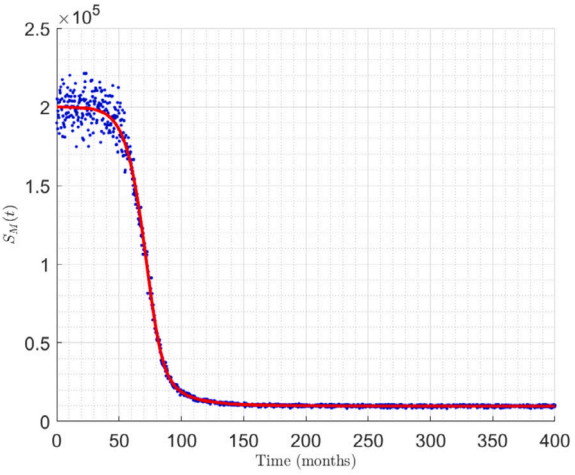
Asymptomatic population



Acute infected population

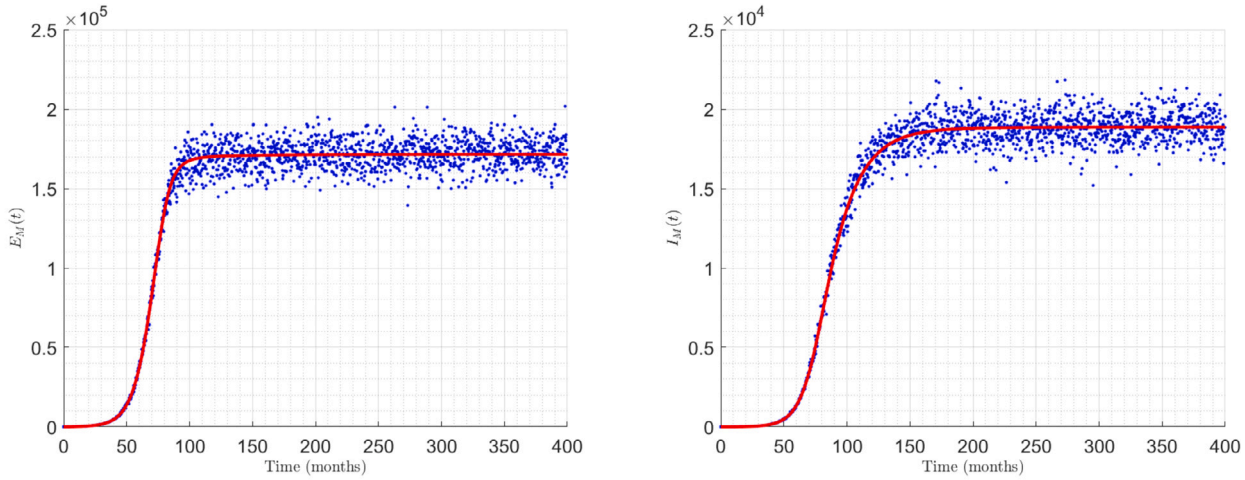


Chronic infected population



Susceptible mosquitoes

Fig. 5. Scatter estimated with standard deviation of 0.05 and numerical simulation (sold) with confidence interval of 95%.



(g) Exposed mosquitoes (h) Infectious mosquitoes

Fig. 6. Scatter estimated with standard deviation of 0.05 and numerical simulation (sold) with confidence interval of 95%.

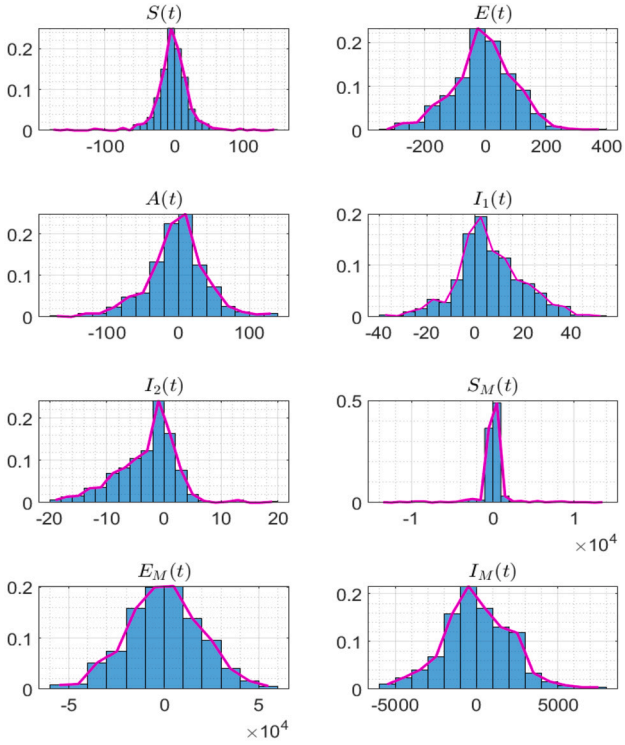


Fig. 7. The residuals of the model outputs.

Fig. 7. The changes in most sensitive parameters have significant variation in both population within the confidence interval of 95% as demonstrated in the Fig. 8

5.2. Conclusion

In this paper, we formulated and analyzed a mathematical model to study the dynamics of lymphatic filariasis in the presence of asymptomatic individuals. We generate data using white noise and parameter values were estimate by least square method. The basic reproduction number $\mathcal{R}_0$ is derived by the next generation matrix approach and sensitivity indices for parameters in $\mathcal{R}_0$ are computed by the normalized forward sensitivity index. Model equilibria were derived and found that, lymphatic free equilibrium is globally asymptotically stable when $\mathcal{R}_0 < 1$ and lymphatic filariasis endemic equilibrium is globally stable when $\mathcal{R}_0 \geq 1$. To gain the

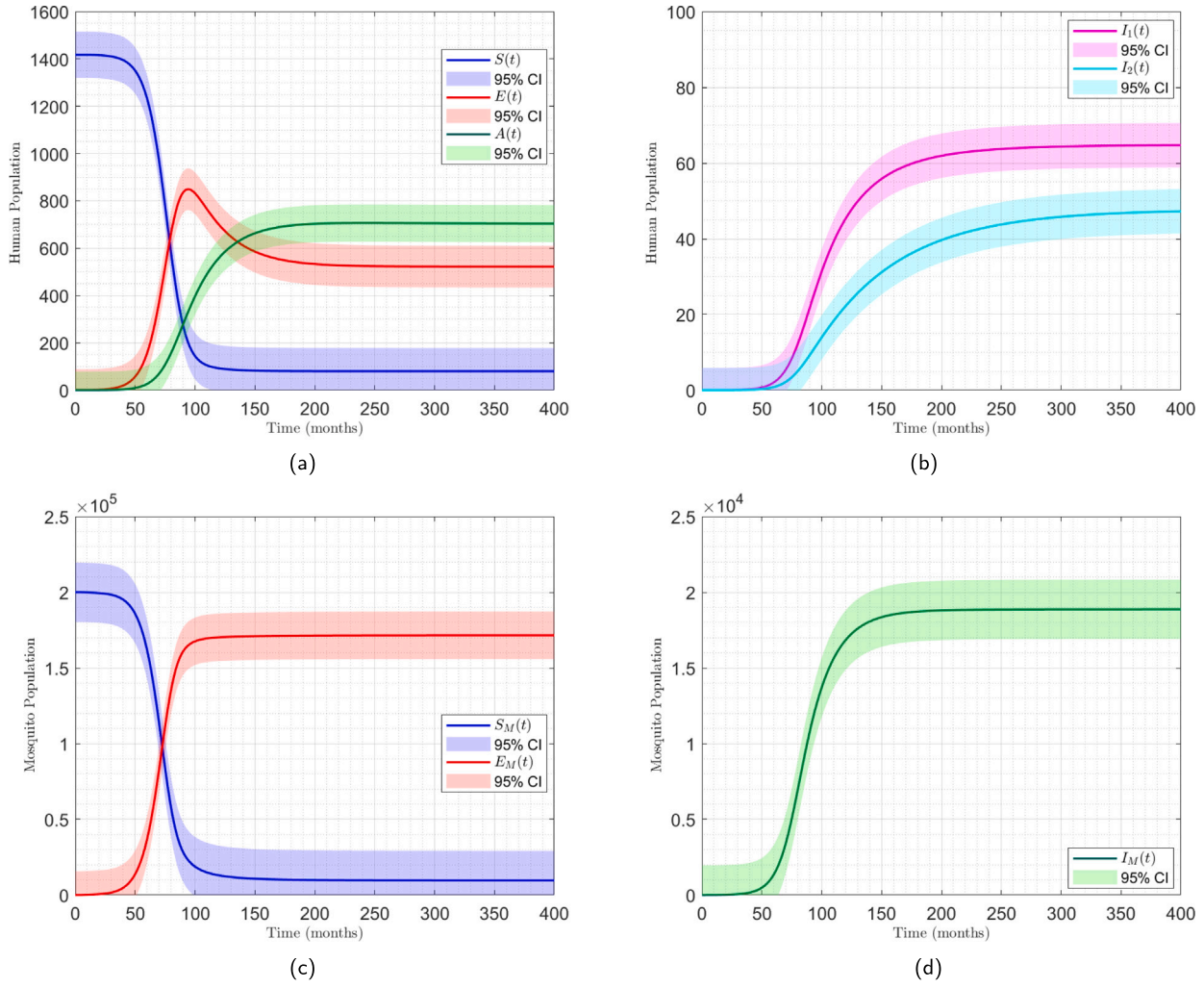


Fig. 8. Simulation of lymphatic filariasis model on dynamics of human populations in (a) and (b) and mosquito populations in (c) and (d), with confidence interval of 95%.

insight into the dynamics of lymphatic filariasis, Latin Hypercube and Partial Rank Correlation Coefficient were used to determine which parameters affect positively or negatively model outputs. Sensitivity analysis shows that, the rate of human infection, and the recruitment rate mosquitoes increase Lymphatic filariasis average new infections. Analysis further shows that asymptomatic individuals contribute significantly in the transmission of lymphatic filariasis.

CRediT authorship contribution statement

(1) Mussa A. Stephano, Maranya M. Mayengo: conception; designed of the study; performed the experiments; analyzed and interpreted the data; contributed reagents, materials, analysis tools or data; and wrote the paper.

(2) Jacob I. Irunde, Dmitry Kuznetsov: Conceived and designed the experiments; performed the experiments; analyzed and interpreted the data and contributed reagents, materials, analysis tools or data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used are included in this paper.

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