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A mathematical model for the dynamics and control of malaria in Nigeria

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ABSTRACT

Malaria is a life-threatening disease endemic in many African countries especially Nigeria. A mathematical model is used to study the dynamics of malaria in Nigeria. The model incorporates drug resistance, treatment, and the use of mosquito nets as preventive strategies. By fitting the model to data on the incidence of malaria in Nigeria, important parameters associated with the disease dynamics are estimated. Using these estimated parameters, the basic reproduction number is calculated, future dynamics simulated, and those parameters with a large impact on Nigerian malaria determined. Overall, the results indicate that the disease is likely to remain endemic in Nigeria unless better control measures are focused on the dominant resistant strain, treatment is improved and the use of mosquito nets become widespread.

1. Introduction

Malaria is a serious illness caused by Plasmodium that are transmitted to human through the bites of infected female Anopheles mosquitoes. Four species of Plasmodium that infect humans are: Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae, and Plasmodium ovale. Plasmodium falciparum and Plasmodium vivax, are the most deadly (WHO, 2022). Plasmodium falciparum, the deadliest malaria parasite, is the dominant malaria parasite on the African continent whereas Plasmodium vivax is the dominant malaria parasite in African countries that are not in the Sub-Sahara (WHO, 2022). The symptoms of malaria include fever, headache and chills etc. Unfortunately, if the disease is left untreated, Plasmodium falciparum malaria can progress to severe illness and death within a period of 24 h (WHO, 2022).

According to the World Health Organization, the cases of malaria are still increasing. For instance, worldwide there were approximately 241 million cases of malaria in 2020 which is high compared to the 227 million cases in 2019 (WHO, 2022). Consequently, the number of deaths due to malaria are also increasing. There were approximately 627 000 malaria deaths in 2020, which is an increase of 69 000 deaths over the previous year (WHO, 2022). A high share of the global malaria burden is in the African region. For instance in 2020, about 95% of all malaria cases and 96% of deaths occurred in the region (WHO, 2022). Unfortunately, children were most affected as about 80% of all malaria deaths in the region were children under 5 years of age. Nigeria is currently one of the African countries with the highest number of cases and deaths due to malaria with about 31.9% of all deaths worldwide (WHO, 2022).

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Malaria has been endemic in Nigeria for a long time, even though the disease is preventable and curable. Treatment failure is a factor that poses a key obstacle to control of malaria in Nigeria (Yusuf et al., 2005). According to Yusuf et al. (2005), non-compliance with treatment is a major factor associated with Nigerian treatment failure of malaria. Treatment failures for malaria have been associated with suboptimal dosages or parasite resistance (Wurtz et al., 2012). Drug resistance against antimalarials is another major hindrance to malaria control (Tumwiine et al., 2014). Also there are increasing reports of drug resistant Plasmodium falciparum throughout the world (Wurtz et al., 2012). Some of the factors that enhance drug resistance of malaria parasites include the following: overuse of antimalarial drugs for prophylaxis, use of fake or substandard drugs, inadequate or incomplete treatments of active infections etc. The National Agency for Food and Drug Administration and Control (NAFDAC) is an federal agency in Nigeria under the Ministry of Health that is in charge of regulating the manufacture, distribution, sale and use of drugs, medical devices, etc. in Nigeria (NAFDAC, 2022). According to NAFDAC, fake drugs are responsible for the growing number of cases of many illnesses in Nigeria (Raufu, 2002). In the present paper, a mathematical model is developed to understand the dynamics of malaria in Nigeria and the impacts of preventative controls.

Mathematical models are tools that have been successfully used to understand the transmission of infectious diseases (Collins & Duffy, 2020; Collins & Duffy, 2021; Collins & Govinder, 2014; Herdicho et al., 2021; Ibrahim & Dénes, 2021; Ojo et al.; Koella & Antia, 2003; Tien & Earn, 2010; Tumwiine et al., 2014). Fitting a mathematical model to real data on a particular disease and subsequently estimating important parameters from the real data can enable researchers to make predictions on the future dynamics of the disease (Kim et al., 2020; Mojeeb et al., 2019; Zhao et al., 2022). Such theoretical study is essential for developing better control measures for proper management of the disease. Several studies have been carried out using mathematical deterministic model to analyse the dynamics and control of malaria (Agusto et al., 2013; Tasman, 2013; Kim et al., 2019; Okuneye & Gumel, 2017; Abiodun et al., 2018; Tumwiine et al., 2014; Herdicho et al., 2021; Tasman, 2015; Koella & Antia, 2003). Importantly, some of these mathematical models have considered the effects of drug resistant as one of the major factors in their studies (Tumwiine et al., 2014; Tasman, 2015; Koella & Antia, 2003). For instance, Tasman (2015) investigated an optimal control strategy to reduce the spread of malaria resistance to anti-malarial drugs using a mathematical model. Koella and Antia (2003) used a mathematical epidemiological model to investigate the spread of anti-malarial resistance. The parameters that are critical in determining the spread of resistant malaria were analysed using their model. Tumwiine et al. (2014) formulated a mathematical model that incorporates evolution of drug resistance and treatment as a preventive strategy to study the spread of drug sensitive and resistant malaria strains. The public health implications of the study were examined using their model.

There is no doubt that those studies have made valuable input in understanding the dynamics and control of malaria. However, as far as we are aware, none of those studies use a mathematical deterministic model that incorporates drug resistant, control measures together with real data to study and make predictions of the possible future dynamics of malaria in Nigeria. This study aims to fill this gap in the literature. The findings from this study are expected to aid both researchers and policy makers in developing better control strategies for effective control and management of malaria outbreaks.

2. Model development

A mathematical model of malaria transmission is developed to study the disease dynamics in Nigeria. The model, in the form of a system of ordinary differential equation, takes into account the major factors responsible for malaria transmission. The model includes a human population $N_h(t)$ and a mosquito population $N_v(t)$ at time t. The human population at time t is partitioned into sub-populations namely: susceptible humans $S(t)$, infected humans $I(t)$, treated humans $T(t)$ and temporary immune humans $R(t)$. To take into account the presence of drug resistant strains, the infected population is further divided into two classes: individuals infected with a resistant strain $I_r(t)$ and individuals infected with a sensitive strain $I_s(t)$. Similarly, the treated humans $T(t)$ are also partitioned into two: treated individuals with a resistant strain $T_r(t)$ and treated individuals with a sensitive strain $T_s(t)$. The mosquito population $N_v(t)$ at time t is also partitioned into susceptible mosquitoes $X(t)$ and infected mosquitoes $Y(t)$.

Other assumptions of the model formulation are as follows. The birth and death rates are equal for both the mosquito and human populations. Consequently, the total population of humans and mosquitoes are constant. Humans recovering from

Table 1
Variables for model (1).

Variables	Meaning
$N_h(t)$	Total human population at time t
$S(t)$	Susceptible humans at time t
$I_r(t)$	Population of humans infected with resistant strains at time t
$I_s(t)$	Population of humans infected with sensitive strains at time t
$T_r(t)$	Treated individuals with resistant strains at time t
$T_s(t)$	Treated individuals with sensitive strains at time t
$R(t)$	Recovered/immune humans at time t
$N_v(t)$	Total mosquitoes population at time t
$X(t)$	Susceptible mosquitoes at time t
$Y(t)$	Population of infected mosquitoes at time t

malaria have temporary immunity against reinfection. The various parameters and their meaning are presented in Table 2. All of the parameter values are assumed to be non-negative. The infection rates are computed as $\beta = \theta\beta_h$, $\alpha_r = \theta\alpha_{rr}$, and $\alpha_s = \theta\alpha_{ss}$, where the parameter θ is the biting rate. In addition, β_h represent the transmission probability from infected mosquitoes to humans. Also, humans infected with the resistant strain $I_r(t)$ transmit malaria to susceptible mosquitoes at a rate α_{rr} and those with the sensitive strain $I_s(t)$ to susceptible mosquitoes at a rate α_{ss}. The number of female Anopheles mosquitoes per human host is denoted by a constant parameter $m = \frac{N_v(t)}{N_h(t)}$ (Agusto et al., 2013; Tumwiine et al., 2014). Humans infected with the resistant strain or sensitive strain are treated at the rates σ_r and σ_s, respectively. Treated individuals $T_r(t)$ and $T_s(t)$ recover at rates γ_r and γ_s, respectively. Drug resistance and other factors such as fake drugs, suboptimal dosages etc. result in treatment failures at rates ϵ_r and ϵ_s, respectively. To take control measures into account, we assume that the use of mosquito nets reduce transmission by a proportion c. Based on these assumptions, the model for malaria transmission is:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \mu N_h(t) - \frac{(1-c)m\beta S(t)Y(t)}{N_v(t)} - \mu S(t) + \omega R(t),\\
\frac{dI_r(t)}{dt} &= \frac{\rho(1-c)m\beta S(t)Y(t)}{N_v(t)} - (\sigma_r + \mu)I_r(t) + \epsilon_r T_r(t),\\
\frac{dI_s(t)}{dt} &= \frac{(1-\rho)(1-c)m\beta S(t)Y(t)}{N_v(t)} - (\sigma_s + \mu)I_s(t) + \epsilon_s T_s(t),\\
\frac{dT_r(t)}{dt} &= \sigma_r I_r(t) - (\gamma_r + \epsilon_r + \mu)T_r(t),\\
\frac{dT_s(t)}{dt} &= \sigma_s I_s(t) - (\gamma_s + \epsilon_s + \mu)T_s(t),\\
\frac{dR(t)}{dt} &= \gamma_r T_r(t) + \gamma_s T_s(t) - (\omega + \mu)R(t),\\
\frac{dX(t)}{dt} &= \xi N_v(t) - \frac{(1-c)\alpha_r X(t)I_r(t)}{N_h(t)} - \frac{(1-c)\alpha_s X(t)I_s(t)}{N_h(t)} - \xi X(t),\\
\frac{dY(t)}{dt} &= \frac{(1-c)\alpha_r X(t)I_r(t)}{N_h(t)} + \frac{(1-c)\alpha_s X(t)I_s(t)}{N_h(t)} - \xi Y(t).
\end{aligned} \tag{1}$$

The meaning of variables and parameters of model (1) can be found in Tables 1 and 2, respectively. A schematic illustration of the malaria model (2) is given in Fig. 1.

The dynamics of this model are investigated by means of dynamical system analysis supported with numerical simulations. Since humans and mosquitoes have different measurement units, a model with dimensionless variables is required. To non-dimensionalize the model (1), we scale the variables using the total population of either humans or mosquitoes where appropriate: $s(t) = \frac{S(t)}{N_h(t)}$, $i_r(t) = \frac{I_r(t)}{N_h(t)}$, $i_s(t) = \frac{I_s(t)}{N_h(t)}$, $\tau_r(t) = \frac{T_r(t)}{N_h(t)}$, $\tau_s(t) = \frac{T_s(t)}{N_h(t)}$, $r(t) = \frac{R(t)}{N_h(t)}$, $x(t) = \frac{X(t)}{N_v(t)}$, $y(t) = \frac{Y(t)}{N_v(t)}$, with $m = \frac{N_v(t)}{N_h(t)}$ a constant. The parameter m denotes the number of female Anopheles mosquitoes per human host. Using these scaled variables the dimensionless version of model (1) becomes

Table 2
Parameters for model (1).

Variables	Meaning	Unit
β	Infection rate from mosquitoes to human	day^{-1}
α_r	Infection rate from $I_r(t)$ to mosquitoes	day^{-1}
α_s	Infection rate from $I_s(t)$ to mosquito	day^{-1}
μ	Natural birth/mortality rate of humans	day^{-1}
ρ	Fraction of humans infected with drug resistant strains	Dimensionless
c	Reduction of infection rate due to use of mosquitoes nets	Dimensionless
σ_r	Treatment rate of $I_r(t)$	day^{-1}
σ_s	Treatment rate of $I_s(t)$	day^{-1}
γ_r	Expected recovery rate of $T_r(t)$	day^{-1}
γ_s	Expected recovery rate of $T_s(t)$	day^{-1}
ϵ_r	Rate of treatment failure for $T_r(t)$	day^{-1}
ϵ_s	Rate of treatment failure for $T_s(t)$	day^{-1}
ω	Wanning immunity rate of $R(t)$	day^{-1}
ξ	Natural birth/death rate of mosquitoes	day^{-1}

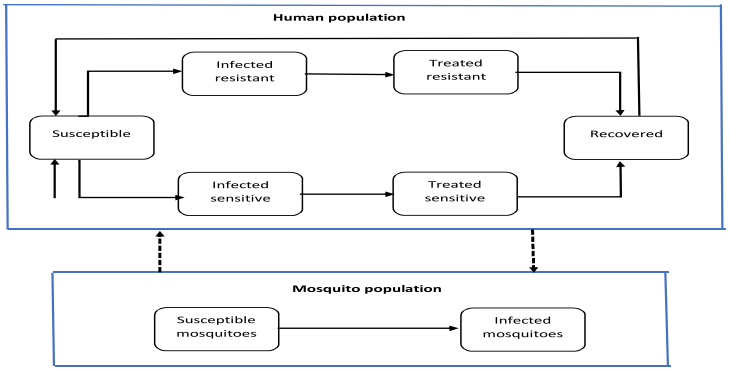

Fig. 1. Schematic illustration of the malaria model (2).

$$
\begin{aligned}
\frac{ds(t)}{dt} &= \mu - (1-c)m\beta s(t)y(t) - \mu s(t) + \omega r(t),\\
\frac{di_r(t)}{dt} &= \rho(1-c)m\beta s(t)y(t) - (\sigma_r + \mu)i_r(t) + \epsilon_r\tau_r(t),\\
\frac{di_s(t)}{dt} &= (1-\rho)(1-c)m\beta s(t)y(t) - (\sigma_s + \mu)i_s(t) + \epsilon_s\tau_s(t),\\
\frac{d\tau_r(t)}{dt} &= \sigma_r i_r(t) - (\gamma_r + \epsilon_r + \mu)\tau_r(t),\\
\frac{d\tau_s(t)}{dt} &= \sigma_s i_s(t) - (\gamma_s + \epsilon_s + \mu)\tau_s(t),\\
\frac{dr(t)}{dt} &= \gamma_r\tau_r(t) + \gamma_s\tau_s(t) - (\omega + \mu)r(t),\\
\frac{dx(t)}{dt} &= \xi - (1-c)\alpha_r x(t)i_r(t) - (1-c)\alpha_s x(t)i_s(t) - \xi x(t),\\
\frac{dy(t)}{dt} &= (1-c)\alpha_r x(t)i_r(t) + (1-c)\alpha_s x(t)i_s(t) - \xi y(t).
\end{aligned}
\tag{2}
$$

For the analyses of model (2) parameters are combined to give $\Lambda = (1-c)m\beta$, $b_r = \sigma_r + \mu$, $b_s = \sigma_s + \mu$, $k_r = \gamma_r + \epsilon_r + \mu$, $k_s = \gamma_r + \epsilon_r + \mu$, $a_r = (1-c)\alpha_r$, $a_s = (1-c)\alpha_s$, $l_r = \gamma_r + \mu$, $l_s = \gamma_s + \mu$.

3. Model analysis

To enhance understanding of the model dynamics, some important mathematical characteristics of model (2) are presented in this section.

3.1. Equilibrium analysis

The disease-free equilibrium (DFE) of model (2) is given by

$$(s^0, i_r^0, i_s^0, \tau_r^0, \tau_s^0, r^0, x^0, y^0) = (1, 0, 0, 0, 0, 0, 1, 0). \tag{3}$$

The basic reproduction number ($\mathcal{R}_0$) of model (2) is calculated using the next-generation matrix method (Van den Driessche & Watmough, 2002). The associated next generation matrix of model (2) are given by

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & \rho\Lambda \\ 0 & 0 & 0 & 0 & (1-\rho)\Lambda \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ a_r & a_s & 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} b_r & 0 & -\epsilon_r & 0 & 0 \\ 0 & b_s & 0 & -\epsilon_s & 0 \\ -\sigma_r & 0 & k_r & 0 & 0 \\ 0 & -\sigma_s & 0 & k_s & 0 \\ 0 & 0 & 0 & 0 & \xi \end{pmatrix}.$$

Consequently,

$$FV^{-1} = \begin{pmatrix} 0 & 0 & 0 & 0 & \frac{\rho\Lambda}{\xi} \\ 0 & 0 & 0 & 0 & \frac{(1-\rho)\Lambda}{\xi} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{a_r k_r}{\sigma_r l_r + \mu k_r} & \frac{a_s k_s}{\sigma_s l_s + \mu k_s} & \frac{a_r \epsilon_r}{\sigma_r l_r + \mu k_r} & \frac{a_s \epsilon_s}{\sigma_s l_s + \mu k_s} & 0 \end{pmatrix}. \tag{4}$$

Thus, the basic reproduction number $\mathcal{R}_0$, which is the spectral radius of the matrix FV^{-1} is calculated as

$$\mathcal{R}_0 = \sqrt{\mathcal{R}_0^r + \mathcal{R}_0^s}, \tag{5}$$

where $\mathcal{R}_0^r = \frac{\rho\Lambda a_r k_r}{\xi(\sigma_r l_r + \mu k_r)}$ and $\mathcal{R}_0^s = \frac{(1-\rho)\Lambda a_s k_s}{\xi(\sigma_s l_s + \mu k_s)}$. Explicitly, $\mathcal{R}_0^r = \frac{(1-c)^2\rho m\beta\alpha_r(\epsilon_r+\gamma_r+\mu)}{\xi[\sigma_r(\gamma_r+\mu)+\mu(\epsilon_r+\gamma_r+\mu)]}$ and $\mathcal{R}_0^s = \frac{(1-c)^2(1-\rho)m\beta\alpha_s(\epsilon_s+\gamma_s+\mu)}{\xi[\sigma_s(\gamma_s+\mu)+\mu(\epsilon_s+\gamma_s+\mu)]}$. The quantities $\mathcal{R}_0^r$ and $\mathcal{R}_0^s$ represent contributions to the basic reproduction number from the resistant and sensitive strains, respectively.

When $\mathcal{R}_0 > 1$, at least one of the following endemic equilibria occur: the resistant strain endemic equilibrium, the sensitive strain endemic equilibrium, or the coexistence endemic equilibrium.

When the resistant strain dominates such that $\mathcal{R}_0^r > 1$ and $\mathcal{R}_0^s \leq 1$, a resistant strain endemic equilibrium exists and is given by

$$(s^*, i_r^*, i_s^*, \tau_r^*, \tau_s^*, r^*, x^*, y^*) = \left(\frac{\mathcal{R}_0^r\mu + \Lambda}{\mathcal{R}_0^r(\mu+\Lambda)}, i_r^*, 0, \frac{\sigma_r i_r^*}{k_r}, 0, r^*, x^*, y^*\right), \tag{6}$$

where $\tau_r^* = \frac{\xi y^*}{a_r(1-y^*)}$, $r^* = \frac{\gamma_r\tau_r^*}{\mu+\omega}$, $y^* = \frac{\mu(1-s^*)}{\Lambda s^*}$ and $x^* = 1 - y^*$.

Similarly, if the sensitive strain dominates such that $\mathcal{R}_0^s > 1$ and $\mathcal{R}_0^r \leq 1$, a sensitive strain endemic equilibrium exists and is given by

$$(s^*, i_r^*, i_s^*, \tau_r^*, \tau_s^*, r^*, x^*, y^*) = \left(\frac{\mathcal{R}_0^s\mu + \Lambda}{\mathcal{R}_0^s(\mu+\Lambda)}, 0, i_s^*, 0, \frac{\sigma_s i_s^*}{k_s}, r^*, x^*, y^*\right), \tag{7}$$

where $i_s^* = \frac{\xi y^*}{a_s(1-y^*)}$, $r^* = \frac{\gamma_s\tau_s^*}{\omega+\mu}$, $y^* = \frac{\mu(1-s^*)}{\Lambda s^*}$ and $x^* = 1 - y^*$.

When the two strains coexist such that $\mathcal{R}_0^r > 1$ and $\mathcal{R}_0^s > 1$, an endemic equilibrium exists with coexistence and is given by

$$(s^*, i_r^*, i_s^*, \tau_r^*, \tau_s^*, r^*, x^*, y^*) = \left(\frac{(\mathcal{R}_0^r + \mathcal{R}_0^s)\mu + \Lambda}{(\mathcal{R}_0^r + \mathcal{R}_0^s)(\mu+\Lambda)}, i_r^*, i_s^*, \tau_r^*, \tau_s^*, r^*, x^*, y^*\right), \tag{8}$$

where $i_r^* = \frac{\xi\mathcal{R}_0^r s^* y^*}{a_r}$, $i_s^* = \frac{\xi\mathcal{R}_0^s s^* y^*}{a_s}$, $\tau_r^* = \frac{\sigma_r i_r^*}{k_r}$, $\tau_s^* = \frac{\sigma_s i_s^*}{k_s}$, $r^* = \frac{\gamma_r\tau_r^* + \gamma_s\tau_s^*}{\omega+\mu}$, $y^* = \frac{\mu(1-s^*)}{\Lambda s^*}$ and $x^* = 1 - y^*$.

The short-term dynamics, as well as the long-term dynamics of an infectious disease model can be determined by the stability of the equilibria (Agusto et al., 2013; Herdicho et al., 2021; Liao & Wang, 2011; Okuneye & Gumel, 2017; Tien & Earn, 2010). For instance in model (2), the stability of the disease-free equilibrium when $\mathcal{R}_0 < 1$, indicates that malaria can be eradicated when $\mathcal{R}_0 < 1$ while stability of the coexistent endemic equilibrium (8) shows that malaria can persist when $\mathcal{R}_0 > 1$. Therefore, to eliminate the disease, conditions under which the basic reproduction number is below unity are crucial.

Theorem 1. *The disease-free equilibrium (3) is globally asymptotically stable when* $\mathcal{R}_0 < 1$.

The proof of this theorem is given in the Appendix section. The epidemiological implication of this theorem is that malaria infections (both resistant and sensitive strains) will be eradicated if $\mathcal{R}_0 < 1$. The challenge is how to keep $\mathcal{R}_0$ below unity so that the disease can be eradicated. In the next section, we will use model (2) together with data from Nigeria to study the dynamics of Nigerian malaria and consequently determine conditions under which the disease could be eradicated.

4. Numerical example: a case study of malaria epidemic in Nigeria

In this section, numerical simulations are considered to explore the dynamics of model (2) using a case study of malaria epidemic in Nigeria.

4.1. Model fitting and parameter estimation

The model is fit and parameters estimated using the actual data of malaria in Nigeria. Malaria has been endemic in Nigeria for many years, so fitting the model (2) to malaria in Nigeria will enable us to make future predictions of the disease dynamics. The incidence of a disease can be defined as the number of new cases per unit of population and is defined here as the number of new cases of malaria per 1000 of the population at risk in Nigeria. Incidence of malaria in Nigeria from 2000 to 2018 taken from The World Bank (2021) and used in this study are given in Fig. 2.

The parameter values used for the numerical simulations together with their sources are given in Table 3.

Since model (2) is non-dimensionalized, to fit the model to the data, we convert the incidence to fractions by dividing by 1000. The transmission rate β is multiplied by a seasonality factor $(1+\cos(\frac{\pi t}{15}))$ to account for irregular seasonal pattern in the data Herdicho et al. (2021). For the model fitting, the parameters in Table 3 are fixed. The unit of most of the parameter values in Table 3 are in per day, but we converted them in per year in the numerical simulations to suit our time scale in the study. Unfortunately, we did not have specific information on the proportions of individuals infected with either the resistance strain or the sensitive strain, and so the model is fit to the total infected population $i_r(t) + i_s(t)$. Parameters that relate to the various control measures are estimated using the fitting algorithm. The algorithm is a built-in MATLAB least-squares fitting routine fmincon from the optimization tool box. Results of the model fit are given in Fig. 3 and show that model (2) is a good fit for incidence of malaria in Nigeria from 2000 to 2018. Hence, the model is used further for predictions of malaria trends in Nigeria.

The remaining parameters are estimated from the model fit and are: $c = 0.1742$, $\sigma_r = 0.0024$ day^{-1}, $\epsilon_r = 0.0055$ day^{-1}, $\sigma_s = 0.0027$ day^{-1} and $\epsilon_s = 0.0006$ day^{-1}. Using these estimated parameters together with the parameters in Table 3, the basic reproduction number $\mathcal{R}_0$ is calculated by substituting these parameter values into equation (5) to obtain $\mathcal{R}_0 = 2.2364$. This value shows that the likelihood is high that malaria is endemic in Nigeria because epidemiologically $\mathcal{R}_0 > 1$ indicates that a disease is likely to be endemic (Tien & Earn, 2010). This results supports previous surveillance report findings that malaria is endemic in Nigeria WHO (2022).

Using the same parameter values, the basic reproduction number $\mathcal{R}_0^r$ for the resistant strain is calculated using a similar approach to be $\mathcal{R}_0^r = 4.3561$. Similarly, the basic reproduction number $\mathcal{R}_0^s$ for the sensitive strain is calculated to be $\mathcal{R}_0^s = 0.6454$. These results show that the resistant strain (Plasmodium falciparum) is the dominant malaria strain and generates more secondary infections in Nigeria. Hence, this resistant strain is currently driving the malaria epidemic in Nigeria.

Using these parameter values the possible long-term dynamics of malaria in Nigeria are shown in Fig. 4. For over a period of fifty years, incidence of malaria remain between 280 and 530 individuals per 1000 at risk of infection. Thus, unless more effective control measures implemented, malaria is likely to remain endemic in Nigeria for many years.

Fig. 3 also shows that the resistance strain ($i_r(t)$) dominates with between 210 and 450 individuals per 1000 at risk of infection in comparison to the sensitive strain ($i_s(t)$) accounting for between 0 and 250 individuals per 1000. This supports our earlier finding that the resistant strain is driving the malaria outbreak in Nigeria.

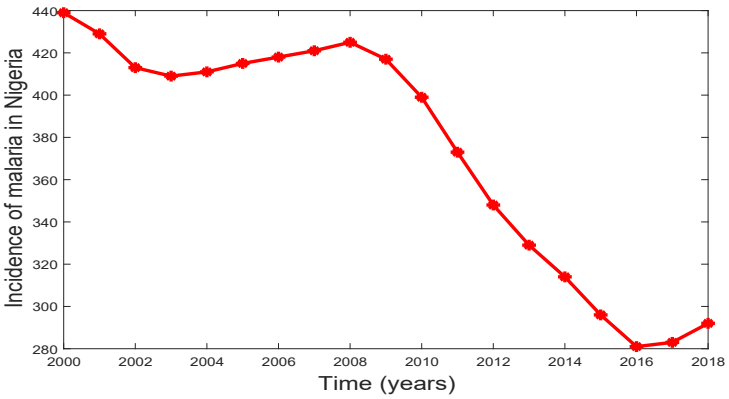

Fig. 2. Plot showing the incidence of malaria per 1000 population at risk in Nigeria from 2000 to 2018 (The World Bank, 2021).

Table 3
Parameters for model (2).

Parameter	Unit	Value	Source
μ	day^{-1}	$\frac{1}{70*365}$	Tasman (2015); Herdicho et al. (2021)
m	dimensionless	variable	Tumwiine et al. (2014)
β	day^{-1}	0.0044	Herdicho et al. (2021); Buonomo and Marca (2018); Rodrigues et al. (2016); Okuneye and Gumel (2017)
ω	day^{-1}	0.005	Herdicho et al. (2021); Abiodun et al. (2018)
ρ	dimensionless	0.3	Tumwiine et al. (2014); Edwards and Biagini (2006)
γ_r	day^{-1}	0.00019	Tumwiine et al. (2014); Barnes and White (2005)
γ_s	day^{-1}	0.0022	Tumwiine et al. (2014); Gemperli et al. (2006)
α_r	day^{-1}	0.0044	Herdicho et al. (2021); Buonomo and Marca (2018); Rodrigues et al. (2016); Okuneye and Gumel (2017)
α_s	day^{-1}	0.0044	Herdicho et al. (2021); Buonomo and Marca (2018); Rodrigues et al. (2016); Okuneye and Gumel (2017)
ξ	day^{-1}	$\frac{1}{15}$	Herdicho et al. (2021); Okuneye and Gumel (2017)

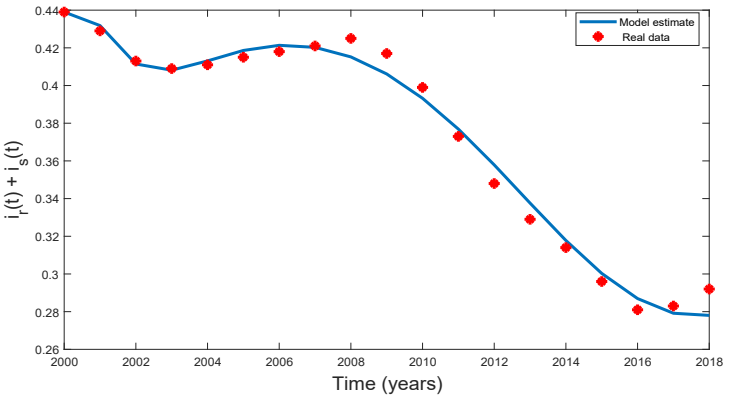

Fig. 3. Model fit of the proportion of incidence of malaria per 1000 population at risk in Nigeria from 2000 to 2018, where bold lines represent the model fit and stars mark the confirm cases.

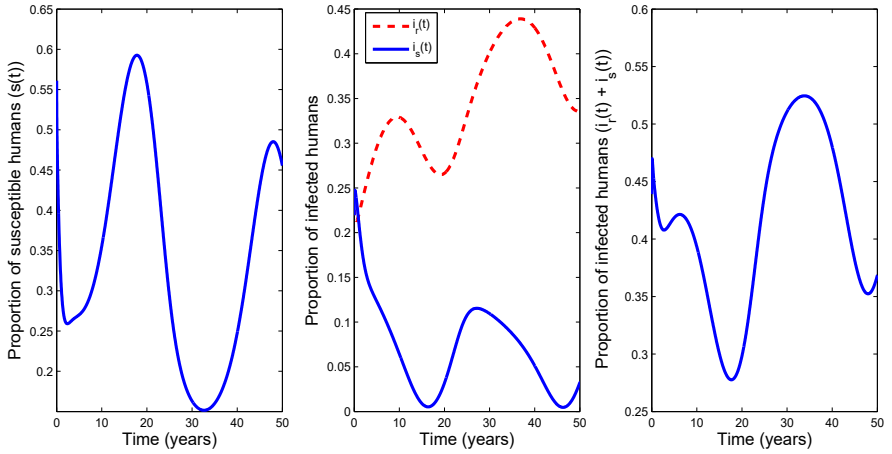

Fig. 4. Plot showing a possible long term dynamics of malaria in Nigeria using the estimated parameter values.

4.2. Effects of control parameters on model dynamics

The impact of each of the control parameters on the human population infected with each strain are investigated by varying the values of each control. As each control is varied the other parameters are kept constant. The effects of altering treatment rates (σ_r, σ_s) are presented in Fig. 5. Increasing σ_r or σ_s up two double the rate does not eradicate the malaria, although for the sensitive strain it is much better.

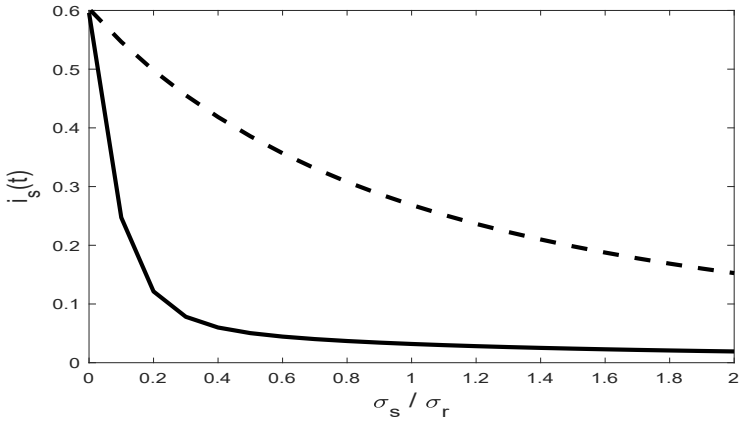

Fig. 5. Plot showing the effects of treatment rates (σ_r, σ_s) on the dynamics of infected humans with the resistant strain (dashed line) and the sensitive strain (solid line).

Fig. 6 shows the effects of treatment failure (ϵ_r, ϵ_s). An increase in treatment failure of the dominant resistant strain results in more infected individuals, especially for the resistant strain.

Another control measure is the use of mosquito nets which have significant effects (Fig. 7). The figure shows that increasing the use of mosquito nets results in a considerable decrease of the incidence of malaria in Nigeria. Depending on the strain, the results are subtly different as might be expected as nets add a slightly better advantage when the strain is easier to cure.

4.3. Sensitivity analysis

In analysing the optimal approach to reduce the negative effects of malaria in Nigeria, it is crucial to understand the significance of the various factors responsible for malaria transmission and prevalence in Nigeria. Studies have shown that initial disease transmission is directly connected to the basic reproduction number $\mathcal{R}_0$ whereas disease prevalence is directly connected with the coexistence endemic equilibrium point, specifically to the magnitudes of i_r^*, i_s^*, and $y*$ (Chitnis et al., 2008). Sensitivity analysis is preferably used to determine the extent to which individual parameter values effect the disease dynamics. Here sensitivity analysis is used to determine which parameters have a significant effect on either of $\mathcal{R}_0$ and the coexistence endemic equilibrium (8).

The Latin Hypercube Sampling Method (LHSM) is considered for the sensitivity analysis. From the LHSM, the partial rank correlation coefficients (PRCCs) of $\mathcal{R}_0$ and the coexistence endemic equilibrium are calculated (see Tables .4 and .5 in the Appendix). The magnitude and sign of the PRCC determine the effect of that parameter on the $\mathcal{R}_0$ or the coexistence endemic equilibrium. For instance, a parameter with a positive PRCC value has the potential of decreasing $\mathcal{R}_0$ when decreased whereas

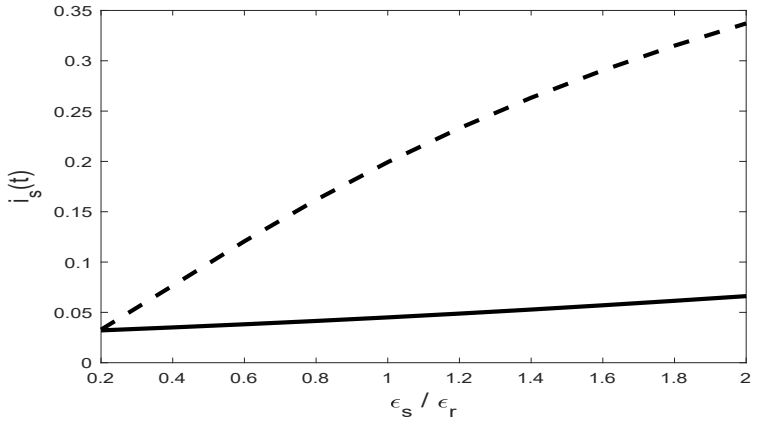

Fig. 6. Plot showing the effects of treatment failure (ϵ_r, ϵ_s) on the dynamics of infected humans with the resistant strain (dashed line) and the sensitive strain (solid line).

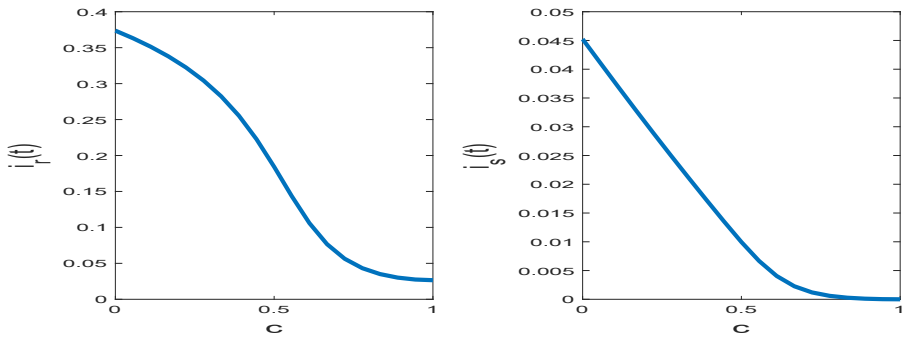

Fig. 7. Plot showing the effects of use of mosquitoes net (c) on the dynamics of infected humans with resistant strain and sensitive strain.

a parameter with a negative PRCC value has the potential of decreasing $\mathcal{R}_0$ when increased. Parameters with PRCC values greater than 0.5 or less than -0.5 are regarded as the most sensitive to $\mathcal{R}_0$ or the coexistence endemic equilibrium Taylor (1990).

To compare the relative importance of each parameter the sensitivity effects (based on the PRCC values) are presented as tornado plots in Fig. 8 for $\mathcal{R}_0$ and Fig. 9 for the coexistence endemic equilibrium.

From Fig. 8 and Table 4, the parameters with the highest influence on the basic reproduction number $\mathcal{R}_0$ in descending order of magnitude of PRCC value are infection rate from mosquitoes to human β, followed by the number of female mosquitoes per human host m, birth/death rate of mosquitoes ξ, the fraction of humans infected with a drug-resistant strain ρ, the infection rate from humans infected with the resistant strain to mosquitoes α_r, treatment rate of humans infected with the resistant strains σ_r, rate of treatment failure for humans infected with a resistant strain ϵ_r, reduction of infection rate due to use of mosquitoes nets c, the expected recovery rate of treated individuals infected with the resistant strain γ_r and natural birth/death rate of humans μ. The remaining parameters which do not have significant influence on $\mathcal{R}_0$ in descending order of PRCC magnitude are σ_s, α_s, ω, ϵ_s and γ_s. From the above results, we observe that the parameters with the highest influence on $\mathcal{R}_0$ are those parameters that are associated with the resistant strains while the remaining parameters with less influence on $\mathcal{R}_0$ are those parameters that are associated with sensitive strains.

Next, we present the results of sensitivity analysis of the coexistence endemic equilibrium from equation (8) using the PRCC. From Fig. 9 and Table 5, the parameters with the highest influence on i_r^* in descending order of magnitude of PRCC values are: ρ, followed by σ_r, ϵ_r, μ and γ_r. The remaining parameters have less influence on i_r^*. Similarly, the parameters with the highest influence on i_s^* in descending order of magnitude of PRCC values are: σ_s, followed by μ, ρ, ϵ_s, and γ_s. The remaining parameters have less influence on i_s^*. From the above results, we observe that the parameter with the highest PRCC values for i_r^* are those parameters associated with the resistance strain while parameters with the highest PRCC values for i_s^* are those parameters associated with the sensitive strain.

For the sensitivity analysis of y^*, the parameters with the highest influence on y^* in descending order of magnitude of PRCC values are birth/death rate of mosquitoes ξ, followed by infection rate from humans infected with the resistant strain to mosquitoes α_r, ρ, μ, σ_r and ϵ_r. The remaining parameters have less influence on y^*. Again, the parameters that have the highest influence are those that are associated with the resistant strain.

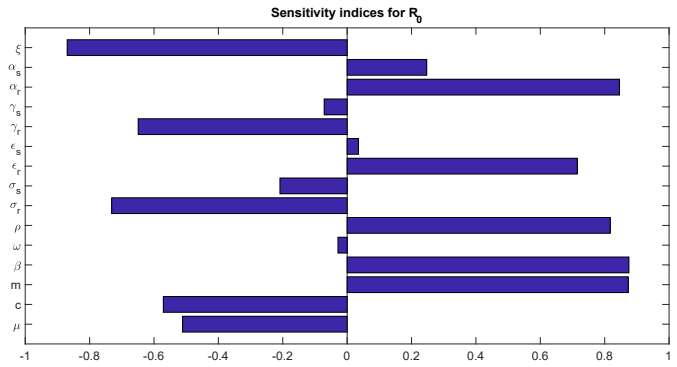

Fig. 8. Tornado plot showing the sensitivity indices for $\mathcal{R}_0$.

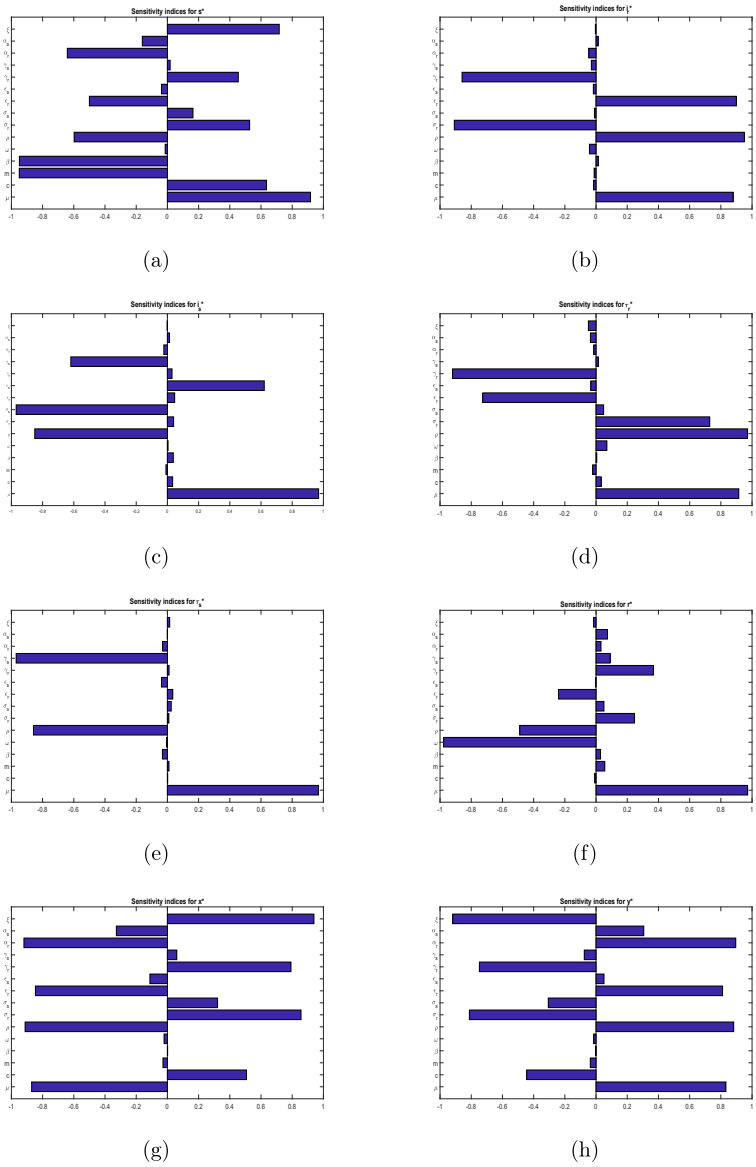

Fig. 9. Tornado plot showing the sensitivity indices of the coexistence endemic equilibrium.

5. Discussion

Malaria has been endemic in many African countries especially in Nigeria which has the highest malaria burden. In this paper, a deterministic model is used to study the transmission dynamics of malaria disease in Nigeria. The model considered drug-resistant strains, treatment, and use of mosquitoes nets on the dynamics. The model is shown to have a unique disease-free equilibrium and three endemic equilibria namely: a resistant strain endemic equilibrium, a sensitive strain endemic equilibrium, and a coexistence endemic equilibrium. The basic reproduction number $\mathcal{R}_0$ of the model was determined using the next-generation matrix method. It is shown that the disease-free equilibrium is globally asymptotically stable when $\mathcal{R}_0 < 1$. This means that malaria disease will be eradicated irrespective of the initial population of the infected individuals when $\mathcal{R}_0 < 1$ otherwise the disease persists.

The model was used to study a malaria epidemic in Nigeria, by fitting it to incidence of malaria from 2000 to 2018. Results show that the model is a good fit for these incidence of malaria. Parameters values that relate to the various control measures (σ_r, σ_s, ϵ_r, ϵ_s, c) are calculated from fitting the model to the data. Using these estimated parameter values together with parameter values from past studies (Table 3), the basic reproduction number $\mathcal{R}_0$ is calculated as $\mathcal{R}_0 = 2.2364$. This result indicates that malaria is endemic in Nigeria in agreement with a surveillance report from the WHO (2022). Using the same

parameter values, the basic reproduction number $\mathcal{R}_0^r$ associated with the resistant strain was calculated as $\mathcal{R}_0^r = 4.3561$ whereas the basic reproduction number $\mathcal{R}_0^s$ associated with the sensitive strain was calculated as $\mathcal{R}_0^s = 0.6454$. These results confirm that the resistant strain is dominant and is driving the Nigerian malaria outbreak. Based on the above results, the resistant strain should be the main target of control measures for the possible eradication of malaria in Nigeria.

Future dynamics of malaria in Nigeria are predicted using model (2) with the parameter values from Table 4 and estimated parameter values. Results from these simulation have some limitations. For instance, most of the parameter values used are constants while in reality they would vary over time. Hence, for a more accurate disease predictions, crucial for public health decisions, variability of the model parameters should be considered. This should be taken into consideration in future research. However, it is still possible to make some important observations by considering simulations of the model in its present form.

From the model dynamics, over the next decades, the incidence in Nigeria could range between 280 and 530 people per 1000 at risk of infection. Based on these findings, malaria is likely to remain endemic in Nigeria for a long period with irregular seasonal variations unless effective control measures, better than the current measures, are implemented. This result is validated by a calculation of the basic reproduction number which is greater than unity. For the dynamics of resistant malaria and sensitive malaria, incidence of individuals infected with the resistance strain ($i_r(t)$) lie between 210 and 450 people per 1000 at risk of infection, while the incidence for individuals infected with the sensitive strain ($i_s(t)$) lie between 0 and 250 people per 1000 at risk of infection. Hence, the proportion of individuals infected with a resistant strain dominates in Nigeria over the period considered. This dominance could be one of the major reasons for the difficulty in controlling malaria in Nigeria.

The possible impacts of the control measures were explored numerically. The effects of both treatment rates, σ_r (for the resistant strain) and σ_s (for the sensitive strain), on the malaria outbreak in Nigeria were considered. Increasing σ_r or σ_s does not result in the eradication of malaria in Nigeria and this is worse for the resistant strain.

The major causes of malaria treatment failure in Nigeria include: fake medicine, drug resistance strains, improper and inadequate application of drugs, etc. Also, non-compliance with treatment has been found to be a major factor associated with treatment failure (Yusuf et al., 2005). From our results an increase in treatment failure leads to an increase in infected individuals but again this is worse for the resistance strain. Based on the model predictions, if nothing is done to reduce the current rate of malaria treatment failure, infected individuals will continue to increase and consequently, malaria will continue to remain endemic in Nigeria. This situation is exacerbated by the dominance of resistance strains.

The impact of the use of mosquito nets were also considered. Increasing the use of mosquito nets significantly decreases the incidence of malaria in Nigeria. Mosquito nets are cost effective and less medically invasive. From these facts and our results, effective use of mosquito nets should be encouraged for possible eradication of malaria in Nigeria.

Finally, sensitivity analyses was used to establish the relative importance of the different factors responsible for malaria transmission and prevalence in Nigeria. Latin Hypercube Sampling method was used to determine the parameters with a high impact on the basic reproduction number $\mathcal{R}_0$ and coexistence endemic equilibrium (8). Five parameters are shown to have a large influence (over 80%) on the basic reproduction number $\mathcal{R}_0$ (Table 4). For example, from the results the infection rate from mosquitoes to human β, the number of female mosquitoes per human host m, and the birth/death rate of mosquitoes ξ, effectively each have an influence of 88% on $\mathcal{R}_0$. These high impact parameters should be the main target to effectively reduce $\mathcal{R}_0$ below unity to enable the eradication of malaria in Nigeria. In a similar manner, the parameters with a high impact on the coexistence endemic equilibrium point are determined (Table 5) and can be targeted for effective control.

Overall, the parameters with the largest influence on $\mathcal{R}_0$, and i_r^* and y^* of the endemic equilibrium point, are those parameters that are associated with the resistant strain. Therefore, control measures must focus on the resistant strain for reducing malaria transmission and prevalence in Nigeria. This result is not surprising as our other analyses also indicate that the resistant strain is the dominant strain driving the malaria outbreak in Nigeria.

Three strong messages result from this study:

- The resistant strain in Nigeria dominates and is a major problem for eradication of the disease.
- Treatment failure is a major part of the Nigerian malaria epidemic.
- The use of mosquito nets could be a cost effective method of limiting malaria outbreaks in Nigeria.

The disease is likely to remain endemic in Nigeria unless control measures are focused on the dominant resistant strain, treatment failure is reduced and the use of mosquito nets becomes widespread.

Declaration of competing interest

The authors declare there are no competing interests regarding the publication of our manuscripts titled “A mathematical model for the dynamics and control of malaria in Nigeria” in the Infectious Disease Modelling.

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Appendix .1. The proof of Theorem 1

The proof of Theorem 1 is established for a special case ($\omega = 0$) using a globally stability results by Castillo-Chavez et al. (2002) which is stated below.

Lemma 1. *Consider a model system written in the form*

$$\begin{aligned} \frac{dZ_1}{dt} &= F(Z_1, Z_2) \\ \frac{dZ_2}{dt} &= G(Z_1, Z_2), \quad G(Z_1, 0) = 0. \end{aligned} \tag{.1}$$

where $Z_1 \in \mathbb{R}^m$, $Z_2 \in \mathbb{R}^n$ and $Z_0 = (Z_1; 0)$ is an equilibrium of the system. Assume that

(H1) *For $\frac{dZ_1}{dt} = F(Z_1, 0)$, Z_1^* is globally asymptotically stable*;
(H2) *$G(Z_1, Z_2) = AZ_2 - \hat{G}(Z_1, Z_2)$, $\hat{G}(Z_1, Z_2) \geq 0$ for $(Z_1, Z_2) \in \Omega$, where the Jacobian $A = \frac{\partial G}{\partial Z_2}(Z_1, 0)$ is a M−matrix (the off diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense.*

Then Z_0 is globally asymptotically stable provided that $\mathcal{R}_0 \leq 1$.

proof. To proof the global stability of model (2), we only need to show that the conditions (*H*1) and (*H*2) hold when $\mathcal{R}_0 \leq 1$. In model (2), let $Z_1 = (s(t), r(t), x(t))$, $Z_2 = (i_r(t), i_s(t), \tau_r(t), \tau_s(t), y(t))$ and $Z_1^* = (1, 0, 1)$. System $G(Z_1, Z_2)$ is given by

$$G(Z_1, Z_2) = \begin{pmatrix} \rho\Lambda s(t)y(t) - b_r i_r(t) + \epsilon_r \tau_r(t) \\ (1-\rho)\Lambda s(t)y(t) - b_s i_s(t) + \epsilon_s \tau_s(t) \\ \sigma_r i_r(t) - k_r \tau_r(t) \\ \sigma_s i_s(t) - k_s \tau_s(t) \\ a_r x(t) i_r(t) + a_s x(t) i_s(t) - \xi y(t) \end{pmatrix}.$$

$G(Z_1, Z_2)$ can be rewritten in the form

$$G(Z_1, Z_2) = AZ_2 - \hat{G}(Z_1, Z_2)$$

where

$$A = \begin{pmatrix} -b_r & 0 & \epsilon_r & 0 & \rho\Lambda \\ 0 & -b_s & 0 & \epsilon_s & (1-\rho)\Lambda \\ \sigma_r & 0 & -k_r & 0 & 0 \\ 0 & \sigma_s & 0 & -k_s & 0 \\ a_r & a_s & 0 & 0 & -\xi \end{pmatrix}$$

and

$$\hat{G}(Z_1, Z_2) = \begin{pmatrix} \rho\Lambda y(t)(1 - s(t)) \\ (1-\rho)\Lambda y(t)(1 - s(t)) \\ 0 \\ 0 \\ a_r i_r(t)(1 - x(t)) + a_s i_s(t)(1 - x(t)) \end{pmatrix}.$$

It is obvious that $\hat{G}(Z_1, Z_2) \geq 0$, since $1 \geq s(t)$ and $1 \geq x(t)$. The global stability of the system

$$\frac{dZ_1}{dt} = F(Z_1, 0) = \begin{pmatrix} \mu - \mu s(t) \\ -\mu r(t) \\ \xi - \xi x(t) \end{pmatrix}$$

can be easily verified as follows: $F(Z_1, 0)$ is a system of linear ordinary differential equations and solving it gives $s(t) = s^0 + B_1 e^{-\mu t}$, $r(t) = r(0)e^{-\mu t}$ and $x(t) = x^0 + B_2 e^{-\xi t}$ where B_1, B_2 are constants. Clearly, $(s(t), r(t), x(t)) \to (s^0, 0, x^0)$. Therefore, Z_1^* is globally asymptotically stable. Hence, DFE is globally asymptotically stable provided $\mathcal{R}_0 \leq 1$. □

Appendix .1. The PRCC values for the sensitivity indices of $\mathcal{R}_0$ and EE (8)

Table 4
The PRCC values for the sensitivity indices of $\mathcal{R}_0$

Parameter	$\mathcal{R}_0$
μ	−0.5315
c	−0.6252
m	0.8787
β	0.8790
ω	−0.0232
ρ	0.8241
σ_r	−0.7415
σ_s	−0.2201
ϵ_r	0.7235
ϵ_s	−0.0223
γ_r	−0.6643
γ_s	−0.0328
α_r	0.8455
α_s	0.2078
ξ	−0.8785

Table 5
The PRCC values for the sensitivity indices of endemic equilibrium (8)

Parameter	s^*	i_r^*	i_s^*	τ_r^*	τ_s^*	r^*	x^*	y^*
μ	0.9066	0.8781	0.9561	0.9069	0.9688	0.9685	−0.8531	0.8705
c	0.6246	−0.0021	0.0041	0.0058	−0.0006	−0.0548	0.4284	−0.4896
m	−0.9421	−0.0070	0.0263	0.0066	−0.0030	0.0478	0.0126	−0.0150
β	−0.9386	0.0138	−0.0391	−0.0106	0.0136	−0.0328	0.0191	0.0375
ω	0.0095	0.0041	0.0138	−0.0198	0.0072	−0.9749	−0.0183	0.0296
ρ	−0.5900	0.9527	−0.8084	0.9674	−0.8523	−0.4658	−0.8963	0.9024
σ_r	0.4877	−0.9079	−0.0089	0.7262	0.0739	0.2259	0.8439	−0.8498
σ_s	0.1493	−0.0175	−0.9578	0.0082	0.0735	0.0358	0.3146	−0.3614
ϵ_r	−0.4903	0.9043	0.0163	−0.7049	−0.0128	−0.2400	−0.8266	0.8391
ϵ_s	−0.0558	0.0129	0.5525	−0.0160	−0.0020	−0.0342	−0.0471	0.0657
γ_r	0.4122	−0.8653	0.0497	−0.9097	−0.0074	0.2930	0.7647	−0.7873
γ_s	0.0291	−0.0357	−0.5267	−0.0142	−0.9680	0.0769	0.0754	−0.0892
α_r	−0.6230	−0.0221	0.0818	0.0138	0.0124	0.0437	−0.9098	0.9169
α_s	−0.1085	0.0648	−0.0119	0.0697	−0.0454	0.0258	−0.3148	0.3726
ξ	0.6727	−0.0024	0.0005	−0.0067	0.0061	−0.0250	0.9299	−0.9354

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