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Bifurcation Analysis of an Age Structured Malaria Model

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Abstract

Malaria is one of the diseases that account for the highest mortality in sub-Saharan Africa particularly among children below the age of five. On 17 April 2023, Nigeria became the second country in the world to approve R21 malaria vaccine to prevent malaria infections in children from five months to thirty-six months of age. In an attempt to investigate the implications of vaccine development for malaria and the subsequent approval of its use in some endemic regions, an age-structured malaria model was designed and some important factors that could shape malaria dynamics were incorporated (e.g. vaccination, nonlinear incidence, asymptomatic carriers, relapse and migration). The validity of the model is established using some mathematics theorems and the reproduction number is computed following the next generation matrix method. Bifurcation analysis is conducted by employing the center manifold theorem. The results of the study indicated that the development of malaria vaccines and the subsequent approval of its use in some malaria endemic regions (e.g. Ghana, Nigeria, etc.) are a welcome development. However, while the vaccines may guarantee the necessary protection, its application and coverage to the fullest may not instigate malaria eradication. The policy implication of the results is that the prevalence of vectors in the endemic regions necessitated adequate vector control in addition to the application of vaccines to minimize malaria transmission.

Keywords: Malaria, vaccines, mathematical model, reproduction number, bifurcation analysis.
MSC2010: 92B05, 34D08, 34D20, 34D23.

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1 Introduction

Malaria is a disease of concern in different countries of the World over the years. The greatest burden of the disease is carried by the Sub-Sahara African-residential human population according to recent reports [1]. However, the low socio-economic and educational status of most people that live in Africa are contributing factors to this burden [2, 3, 4]. Also, climatic conditions such as wind, rainfall, relative humidity, and temperature; obtainable in Africa accelerate the survival and reproduction rate of the malaria vector [5, 6, 7]. The Plasmodium falciparum specie is the predominant malaria infection parasite in the Sub-Sahara African region in contrast to other endemic regions of the World [8, 9, 10]. Malaria is an acute illness, causing symptoms such as, fever, headache, and chills and vomiting. Although malaria is preventable and treatable, the disease can lead to death if left untreated [11]. Despite the efforts to prevent, control, and eradicate the disease, malaria remains a public health problem globally and mainly in the tropics and subtropics region [12]. It is also estimated that between 300 and 500 million individuals are infected annually, with most of the estimated cases observed in Asia, Africa, Latin America, the Middle East and some parts of Europe [13]. In 2018, an estimated 228 million cases of malaria and 405,000 deaths from malaria occurred worldwide with 93% of all malaria cases and 94% of all malaria deaths occurred in the African region [1].

In 2019, malaria was estimated to be 229 million cases and 409,000 deaths worldwide [14]. The disease is more severe in children under five years old, with two-thirds of the reported deaths being children [15]. Malaria is also a serious parasitic disease in less developed countries causing a high mortality. It is estimated that nearly 300 to 400 million malaria cases occur worldwide, out of which 1.5 to 2 million die every year [15]. In Nigeria, an estimated 76 percent of Nigeria's population is at risk of malaria by living in high transmission areas. Nigeria accounts for 27 percent of malaria cases worldwide and the highest number of malaria deaths (24 %) in 2019 [13].

Several factors contribute to malaria transmission. These include infected migrants, asymptomatic carriers and age. Malaria burden depends on the age-structure of the human population as children bear more burden than adults [14]. Children are more vulnerable to malaria than adults since they have not developed immunity to infections [16]. It is estimated that two-third of the world malaria deaths occurs in children less than five years of age [14].

Asymptomatic infections also play crucial roles in the dynamics of malaria. Asymptomatic infections occur as a result of repeated exposure to disease [17]. The asymptomatic carriers serve as a reservoir of parasites for malaria transmission [18]. Asymptomatic carriers present the case of a human individual who harbors the parasite capable of transmitting the disease, but without exhibiting symptoms. Also, there is a direct relationship between disease dynamics and human movement patterns. The global increase in human mobility is creating highly favorable conditions for the persistence of diseases being targeted for elimination, such as malaria, and for the faster spread of emerging pathogens, such as Ebola or Zika [19, 20].

Mathematical models can improve our understanding of the epidemiology of malaria and those components that are significant to malaria diagnosis, treatment and control. [21, 22]. Mathematical models have been used for many years to understand the mechanisms of malaria transmission, since such models approach can be used to give a visual interpretation of any possible intervention that can be implemented in the field to control malaria transmission. These approaches provide a scientific background before a final decision from the government should be taken. Based on the importance of mathematical models on the epidemiological study of malaria, a good number of papers have been developed across the globe by the scholars.

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From the early work by Ross in 1911 [23], many mathematical models were introduced by authors to help a better understanding of malaria transmission. Macdonald in 1957 did some modifications to Ross's model by including superinfection and used his model to estimate the infection and recovery rates of malaria [24]. He found that reducing the number of mosquitoes in an endemic area is an inefficient malaria control strategy. In the early 1980s–1990s, Aron and May and Anderson and May constructed their malaria models based on the assumptions that immunity to malaria is independent of the duration of exposure [25, 26]. Okosun and other researchers concluded from their mathematical model that a combination of insecticides and transmission-blocking treatment is the most cost-effective interventions to control malaria [27]. An optimal vaccination and bed net mathematical model is introduced by [28]. Their analytical results reveal that increasing the case detection strategy may reduce the chance of backward bifurcation phenomena in their model. An analysis of the potential impact of pre-erythrocytic vaccine from clinical data was discussed by the author in [15].

Similar to [28], [14] also found a possible backward bifurcation from their model on the impact of transmission-blocking drugs. Their model projects an approximately 82% malaria death rate reduction by 2035 if 35% of the population in Sub-Saharan Africa receives a transmission-blocking drug with an efficacy of 95%. [29] analyzed the dynamics of malaria using incidence data in Bangladesh from 2001 to 2014. They found that as infection rate had the greatest impact on the basic reproduction number compared to other model parameters, it was important to reduce the infection rate which could be achieved by using insecticide-treated bed nets, spraying insecticides, clearing stagnant water, etc. In a more recent mathematical model, authors include more recent facts on malaria transmission such as the effect of vector-bias [30], asymptotic carriers [31], age-structured [12, 32, 33, 34], competitive strains [35], seasonal factors [36, 37], and coinfection of malaria with COVID-19 [38]. Furthermore, intervention models also have been widely introduced by authors, such as the use of fumigation [39], insecticide-treated bed nets [40], and vaccines with waning immunity [41], or transmission-blocking vaccines [42].

While there have been several works on malaria, only few focuses on age-structured, infected immigrants, nonlinear incidence rate and vaccinated group. Most existing age-structured malaria models adopt standard incidence rate to model malaria transmission [12, 32, 33, 34] . Besides, none of the models consider vaccination as a malaria control strategy. Also, infected immigrants are not well captured in some of the models that incorporated them [12, 32, 33, 34]. However, infected immigrants are important components of malaria dynamics. Their presence can trigger reemergence of malaria in an area where it has previously been eradicated. Their presence can also worsen malaria transmission in already endemic regions. Further, in modeling disease spread, nonlinear incidence rate is more reasonable than the standard incidence rate because it includes the behavioral change and crowding effect of the infective individuals and prevents the unboundedness of the contact rate by choosing suitable parameters [43, 44, 45].

Lastly, in 2015, Glaxo-SmithKline's (GSK's) *RTS, S/AS01* pre-erythrocytic vaccine received a positive scientific response on the quality of this vaccine in combating malaria transmission [46]. Recently, Ghana and Nigeria recognized the impacts of vaccines in combating the spread of malaria and approved the R21 malaria vaccine manufactured by the Serum Institute of India [47]. The vaccine is developed at the University of Oxford and is indicated for the prevention of clinical malaria in children from 5 months to 36 months of age [47]. Based on the emergence of various vaccines and the development of pre-erythrocytic vaccine (*RTS, S/AS01*) in particular, [1] developed a mathematical model to study the potential impact of pre-erythrocytic vaccine (*RTS, S/AS01*) as a control strategy to reduce the spread of malaria.

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This study is motivated to fill the existing gaps in some age-structured malaria models - [12, 32, 33, 34] by incorporating infected immigrants, nonlinear incidence rate and the influence of vaccines on malaria dynamics. The study is intended to conduct the bifurcation analysis to investigate the strength vaccines in combating malaria so as to inform the policy makers the extent of reliability of malaria vaccines in the fight against malaria eradication.

2 MODEL FORMULATION

The model with human and vector compartments are formulated. The human population $N_h(t)$ is divided into two classes, children $N_c(t)$ and adults $N_a(t)$; that is $N_h(t) = N_c(t) + N_a(t)$. The children class is a subgroup of the host population whose members are less than five years old. These members are vulnerable to malaria. The adult class is the group of individuals aged five years and above who are less vulnerable to malaria. Each group is further subdivided into five classes; vaccinated children $(V_c(t))$, susceptible children $(S_c(t))$, asymptomatic children $(A_c(t))$, infected children $(I_c(t))$, recovered children $(R_c(t))$, vaccinated adults $(V_a(t))$, susceptible adults $(S_a(t))$, asymptomatic adults $(A_a(t))$, infected adults $(I_a(t))$ and recovered adults $(R_a(t))$, so that

$$N_h(t) = V_c(t) + S_c(t) + A_c(t) + I_c(t) + R_c(t) + V_a(t) + S_a(t) + A_a(t) + I_a(t) + R_a(t). \quad (2.1)$$

The population of vector at time t, denoted by $N_v(t)$, is sub-divided into mutually-exclusive compartments of susceptible vector $(S_v(t))$ and infected vector $(I_v(t))$ so that

$$N_v(t) = S_v(t) + I_v(t). \quad (2.2)$$

The transmissions across the compartments are illustrated in Figure 1

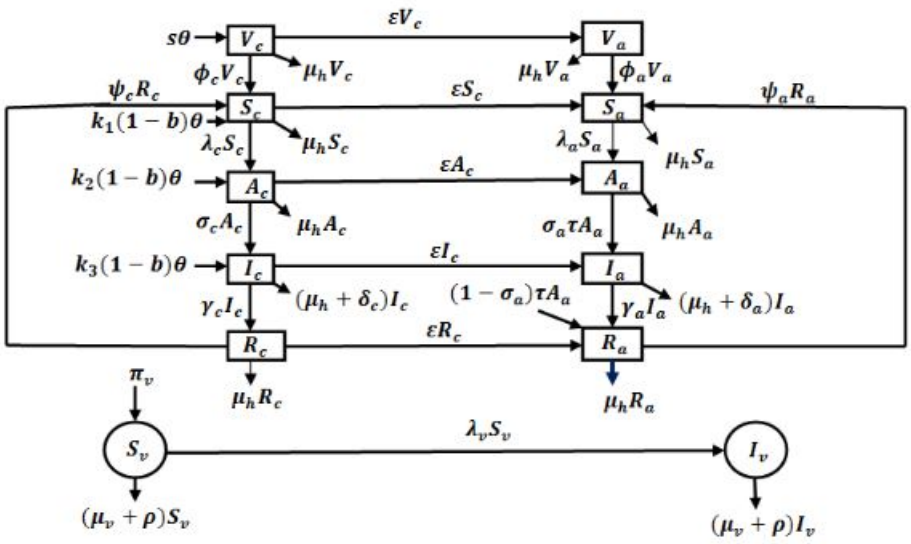

Figure 1: Transmission diagram of malaria in human and vector populations.

IJMSO

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Since the model captures infected immigrants and the influence of vaccination on malaria dynamics, recruitment rate in Figure **??** which is either by birth or by migration occurs at rate θ with $b\theta$, $k_1(1-b)\theta$, $k_2(1-b)\theta$ and $k_3(1-b)\theta$ recruited into $V_c(t)$, $S_c(t)$, $A_c(t)$ and $I_c(t)$ respectively. The vaccinated children $V_c(t)$ moves to the susceptible class at the expiration of immunity at rate ϕ_c. Susceptible children $S_c(t)$ become infected and join the asymptomatic group $A_c(t)$ upon bitten by infectious vectors $I_v(t)$ with force of infection λ_c. Because of the recent approval of vaccines in preventing clinical malaria in children from 5 months to 36 months of age [48], vaccination is introduced to the susceptible children and it is assumed that the force of infection is reduced by the constant $(1-m)$, where m is the rate of vaccination of susceptible children. $S_c(t)$ class however gains individuals at rate ψ_c when there is a relapse after malaria cure. Asymptomatic children $A_c(t)$ develop malaria symptoms at rate σ_c and move to the infectious compartment $I_c(t)$. Infectious children $I_c(t)$ however recover from malaria infection through treatment and join recovered class at rate γ_c. Children mature into adults at the same rate ε. Vaccinated adults $V_a(t)$ lose immunity and become susceptible at rate ϕ_a. Susceptible adults $S_a(t)$ become infected when they are bitten by infectious vector $I_v(t)$ with force of infection λ_a and join the asymptomatic group $A_a(t)$. Because of vigor and immunity in adults, the proportion $(1-\sigma_a)$ from $A_a(t)$ joins the recovered class before the symptoms appear while the remaining proportion σ_a join the infectious class, both at the same rate τ. Infectious adults $I_a(t)$ however recover from malaria infection through treatment and join recovered class at rate γ_a. All the compartments (both children and adults) lose population to natural deaths at the same rate μ_h while in addition to natural deaths, infectious children and adults compartments $I_c(t)$ and $I_a(t)$ lose populations to malaria at rates δ_c and δ_a respectively.

As for the vector population, susceptible vectors $S_v(t)$ are recruited at rate π_v but become infected and join the compartment for the infectious vectors $I_v(t)$ with force infection λ_v when they come in contact with infectious humans (i.e., $A_c(t)$, $I_c(t)$, $A_a(t)$ or $I_a(t)$). Natural deaths and deaths due to vector control occur in the vector populations at the same rate μ_v and ρ respectively. The model is built around the following main assumptions.

1. Malaria spread is attributed only to horizontal transmission;

2. Individuals in the vaccinated class have temporary immunity against malaria infection;

3. Vaccination in susceptible children does not proffer total protection but it reduces effective contact;

4. Asymptomatic adults may recover from malaria before symptoms development;

5. Every individual below the age of five is a child while any person aged five and above is an adult;

6. Malaria transmission to susceptible vectors $S_v(t)$ is higher from infectious humans $I_c(t)$ and $I_a(t)$ than from asymptomatic humans $A_c(t)$ and $A_a(t)$.

Following the aforementioned assumptions, formulations and the flow diagram, the age-structured model for the transmission dynamics of malaria in a community is given by the following determin-

IJMSO

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istic system of non-linear differential equations:

$$\frac{dV_c}{dt} = b\theta - (\phi_c + \varepsilon + \mu_h)\, V_c, \tag{2.3}$$

$$\frac{dV_a}{dt} = \varepsilon V_c - (\mu_h + \phi_a)\, V_a, \tag{2.4}$$

$$\frac{dS_c}{dt} = k_1 (1-b)\, \theta + \phi_c V_c + \psi_c R_c - \lambda_c S_c - (\mu_h + \varepsilon)\, S_c, \tag{2.5}$$

$$\frac{dS_a}{dt} = \varepsilon S_c + \phi_a V_a + \psi_a R_a - \lambda_a S_a - \mu_h S_a, \tag{2.6}$$

$$\frac{dA_c}{dt} = k_2 (1-b)\, \theta + \lambda_c S_c - (\sigma_c + \varepsilon + \mu_h)\, A_c, \tag{2.7}$$

$$\frac{dA_a}{dt} = \varepsilon A_c + \lambda_a S_a - (\tau + \mu_h)\, A_a, \tag{2.8}$$

$$\frac{dI_c}{dt} = k_3 (1-b)\, \theta + \sigma_c A_c - (\delta_c + \gamma_c + \varepsilon + \mu_h)\, I_c, \tag{2.9}$$

$$\frac{dI_a}{dt} = \varepsilon I_c + \sigma_a \tau A_a - (\delta_a + \gamma_a + \mu_h)\, I_a, \tag{2.10}$$

$$\frac{dR_c}{dt} = \gamma_c I_c - (\psi_c + \varepsilon + \mu_h)\, R_c, \tag{2.11}$$

$$\frac{dR_a}{dt} = (1-\sigma_a)\tau A_a + \varepsilon R_c + \gamma_a I_a - (\psi_a + \mu_h) R_a, \tag{2.12}$$

$$\frac{dS_v}{dt} = \pi_v - \lambda_v S_v - (\mu_v + \rho) S_v, \tag{2.13}$$

$$\frac{dI_v}{dt} = \lambda_v S_v - (\mu_v + \rho) I_v, \tag{2.14}$$

where k_1, k_2, k_3 are constants such that $k_1 + k_2 + k_3 = 1$ with nonnegative initial conditions

$$V_c(0) > 0,\ S_c(0) \geq 0,\ V_a(0) \geq 0,\ S_a(0) \geq 0,\ A_c(0) > 0, I_c(0) > 0, R_c(0) \geq 0\ ,$$

$$A_a(0) \geq 0,\ I_a(0) \geq 0,\ R_a(0) \geq 0,\ S_v(0) > 0,\ I_v(0) \geq 0\ .$$

Also, $\lambda_c = \frac{n(1-m)\beta_c I_v}{I_v + \vartheta}$, $\lambda_a = \frac{n\beta_a I_v}{I_v + \vartheta}$ and $\lambda_v = \frac{n\beta_v[\eta(A_c + A_a) + I_c + I_a]}{(A_c + A_a + I_c + I_a) + \varphi}$.

The variables and parameters for the model are redefined in Table 1 and Table 2 for ease of reference

Table 1. description of model variables

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
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Variables	Descriptions
V_c	Population of vaccinated children
S_c	Population of susceptible children
V_a	Population of vaccinated adults
S_a	Population of susceptible adults
A_c	Population of asymptomatic children
I_c	Population of symptomatic children
R_c	Population of recovered children
A_a	Population of asymptomatic adults
I_a	Population of symptomatic adults
R_a	Population of recovered adults
S_v	Population of susceptible vectors
I_v	Population of infectious vectors

Table 2. description of model parameters

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055

Parameters	Descriptions
μ_h	Natural death rate for humans
δ_c	Disease-induced mortality rate for children
δ_a	Disease-induced mortality rate for adults
θ	Human recruitment rate
π_v	Recruitment rate for vector
μ_v	Natural death rate for vector
ρ	Death rate for vector due to control
β_c	Probability that the mosquito bites result in malaria for children
β_a	Probability that the mosquito bites result in malaria for adults
β_v	Probability of infection of susceptible vectors per bite of the infected host
n	Average per capita biting rate of mosquitoes
m	Vaccination rate of susceptible children
ϕ_c	Waning rate of immunity acquired through immunization for children
ϕ_a	Waning rate of immunity acquired through immunization for adults
ε	Maturation rate for children
ψ_c	Rate of loss of natural immunity for children
ψ_a	Rate of loss of natural immunity for adults
b	Proportion of children recruited initially
σ_c	Rate of development of clinical symptoms of malaria for asymptomatic children
σ_a	Rate of development of clinical symptoms of malaria for asymptomatic adults
η	Modification parameter for reduction in infectiousness of asymptomatic humans
γ_c	Recovery rate for children
γ_a	Recovery rate for adults
τ	Rate of progression from asymptomatic stage for adults
ϑ	Rate of control of mosquitoes
φ	Rate of effectiveness of malaria prevention/ treatment
k_1, k_2, k_3	Ratios of the children recruited to the susceptible, asymptomatic and infectious compartments respectively

The model (2.3-2.14) is a modification and an extension of malaria models developed in [12, 32, 33, 34] by including:

1. the impacts of vaccination on malaria dynamics;

2. proportions of infected immigrants;

3. natural recovery rate for asymptomatic adults
   and;

4. non-linear incidence rate.

IJMSO

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The model shall be studied qualitatively. Emphasis shall be placed on the bifurcation and sensitivity of the model parameters to determine the major parameters to be targeted for control of malaria particularly in the endemic regions.

Before the model is applied, it is necessary to show that it is epidemiologically and mathematically well-behaved to guarantee its usability. The existence and uniqueness, positivity and boundedness properties of solutions for the model shall be examined to verify its applicability.

2.1 Existence and Uniqueness of Solutions of (2.3-2.14)

Theorem 1 [48]. *Let* Ω *denote a region*

$/t- t_0/ \leq y$, $''\|x - x_0\|'' \leq z$, $x = (x_1, x_2, \ldots, x_n)$, $x_0 = (x_{10}, x_{20}, \ldots, x_{n0})$.

Also, suppose the Lipschitzian condition $''\|f(t, x_1) - f(t, x_2)\|'' \leq c''x_1 - x_2''$ *is satisfied by* f (t, x), *whenever* (t, x_1) *and* (t, x_2) *is in* Ω, *where* c *is positive. A unique continuous vector solution* $x(t)$ *of the system in the interval* $t- t_0 \leq \delta$ *exists, such that* $\delta > 0$.

Proof. Let Ω denote the region $0 \leq \alpha \leq R$, we want to show that the partial derivatives of (2.3-2.14) are continuous and bounded in Ω. Let

$$H_1 = b\theta - (\phi_c + \varepsilon + \mu_h) V_c,$$

$$H_2 = \varepsilon V_c - (\mu_h + \phi_a) V_a,$$

$$H_3 = k_1 (1 - b) \theta + \phi_c V_c + \psi_c R_c - \lambda_c S_c - (\mu_h + \varepsilon) S_c,$$

$$H_4 = \varepsilon S_c + \phi_a V_a + \psi_a R_a - \lambda_a S_a - \mu_h S_a,$$

$$H_5 = k_2 (1 - b) \theta + \lambda_c S_c - (\sigma_c + \varepsilon + \mu_h) A_c,$$

$$H_6 = \varepsilon A_c + \lambda_a S_a - (\tau + \mu_h) A_a,$$

$$H_7 = k_3 (1 - b) \theta + \sigma_c A_c - (\delta_c + \gamma_c + \varepsilon + \mu_h) I_c,$$

$$H_8 = \varepsilon I_c + \sigma_a \tau A_a - (\delta_a + \gamma_a + \mu_h) I_a,$$

$$H_9 = \gamma_c I_c - (\psi_c + \varepsilon + \mu_h) R_c,$$

$$H_{10} = (1 - \sigma_a)\tau A_a + \varepsilon R_c + \gamma_a I_a - (\psi_a + \mu_h) R_a,$$

$$H_{11} = \pi_v - \lambda_v S_v - (\mu_v + \rho) S_v,$$

$$H_{12} = \lambda_v S_v - (\mu_v + \rho) I_v,$$

Then the partial derivatives of $(H_1 - H_{12})$ are given below as

$\left|\frac{\partial H_1}{\partial V_c}\right| = |-(\phi_c + \varepsilon + \mu_h)| < \infty$; ∂H_1 w.r.t. ∂ of other variables $= |0| < \infty$.

$\left|\frac{\partial H_2}{\partial V_c}\right| = |\varepsilon| < \infty$; $\left|\frac{\partial H_2}{\partial V_a}\right| = |-(\phi_a + \mu_h)| < \infty$; ∂H_2 w.r.t. ∂ of other variables $= |0| < \infty$.

$\left|\frac{\partial H_3}{\partial V_c}\right| = |\phi_c| < \infty$; $\left|\frac{\partial H_3}{\partial R_c}\right| = |\psi_c| < \infty$; $\left|\frac{\partial H_3}{\partial S_c}\right| = |-(\lambda_c + \mu_h + \varepsilon)| < \infty$; ∂H_3 w.r.t. ∂ of other variables $= |0| < \infty$.

$\left|\frac{\partial H_4}{\partial S_c}\right| = |\varepsilon| < \infty$; $\left|\frac{\partial H_4}{\partial V_a}\right| = |\phi_a| < \infty$; $\left|\frac{\partial H_4}{\partial R_a}\right| = |\psi_a| < \infty$; $\left|\frac{\partial H_4}{\partial S_a}\right| = |-(\lambda_a + \mu_h)| < \infty$; ∂H_4 w.r.t. ∂ of other variables $= |0| < \infty$.

$\left|\frac{\partial H_5}{\partial S_c}\right| = |\lambda_c| < \infty$; $\left|\frac{\partial H_5}{\partial A_c}\right| = |-(\sigma_c + \varepsilon + \mu_h)| < \infty$; ∂H_5 w.r.t. ∂ of other variables $= |0| < \infty$.

$\left|\frac{\partial H_6}{\partial V_c}\right| = |\varepsilon| < \infty$; $\left|\frac{\partial H_6}{\partial S_a}\right| = |\lambda_a| < \infty$; $\left|\frac{\partial H_6}{\partial A_a}\right| = |-(\tau + \mu_h)| < \infty$; ∂H_6 w.r.t. ∂ of other variables $= |0| < \infty$.

IJMSO

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$\left|\frac{\partial H_7}{\partial A_c}\right| = |\sigma_c| < \infty$; $\left|\frac{\partial H_7}{\partial I_c}\right| = |-(\delta_c + \gamma_c + \varepsilon + \mu_h)| < \infty$; ∂H_7 w.r.t. ∂ of other variables $= |0| < \infty$.
$\left|\frac{\partial H_8}{\partial I_c}\right| = |\varepsilon| < \infty$; $\left|\frac{\partial H_8}{\partial A_a}\right| = |\sigma_a| < \infty$; $\left|\frac{\partial H_8}{\partial I_a}\right| = |-(\delta_a + \gamma_a + \mu_h)| < \infty$; ∂H_8 w.r.t. ∂ of other variables $= |0| < \infty$.
$\left|\frac{\partial H_9}{\partial I_c}\right| = |\gamma_c| < \infty$; $\left|\frac{\partial H_9}{\partial R_c}\right| = |-(\psi_c + \varepsilon + \mu_h)| < \infty$; ∂H_9 w.r.t. ∂ of other variables $= |0| < \infty$.
$\left|\frac{\partial H_{10}}{\partial A_a}\right| = |1 - \sigma_a|\tau < \infty$; $\left|\frac{\partial H_{10}}{\partial R_c}\right| = |\varepsilon| < \infty$; $\left|\frac{\partial H_{10}}{\partial I_a}\right| = |\gamma_a| < \infty$; $\left|\frac{\partial H_{10}}{\partial R_a}\right| = |-(\psi_a + \mu_h)| < \infty$; ∂H_{10} w.r.t. ∂ of other variables $= |0| < \infty$.
$\left|\frac{\partial H_{11}}{\partial S_v}\right| = |-(\lambda_v + \mu_v + \rho)| < \infty$; ∂H_{11} w.r.t. ∂ of other variables $= |0| < \infty$.
$\left|\frac{\partial H_{12}}{\partial S_v}\right| = |\lambda_v| < \infty$; $\left|\frac{\partial H_{12}}{\partial I_v}\right| = |-(\mu_v + \rho)| < \infty$; ∂H_{12} w.r.t. ∂ of other variables $= |0| < \infty$.
Given the above partial derivatives of $(H_1 - H_{12})$ w.r.t. each variables, it is shown that the partial derivatives of (2.3-2.14) exists, are finite and bounded. Hence (2.3-2.14) has a unique solution.

Theorem 2. The solutions of the model are positive and bounded for all $t \geq 0$ if the model's initial conditions are all nonnegative
(i.e., $V_c(0) > 0,\ S_c(0) \geq 0,\ V_a(0) \geq 0,\ S_a(0) \geq 0,\ A_c(0) > 0, I_c(0) > 0, R_c(0) \geq 0$,

$$A_a(0) \geq 0,\ I_a(0) \geq 0,\ R_a(0) \geq 0,\ S_v(0) > 0,\ I_v(0) \geq 0).$$

Proof.

$$\frac{dV_c}{dt}\Big| V_c = 0 = b\theta,$$

$$\frac{dS_c}{dt}\Big| S_c = 0 = k_1(1-b)\theta + \phi_c V_c + \psi_c R_c,$$

$$\frac{dV_a}{dt}\Big| V_a = 0 = \varepsilon V_c,$$

$$\frac{dS_a}{dt}\Big| S_a = 0 = \varepsilon S_c + \phi_a V_a + \psi_a R_a,$$

$$\frac{dA_c}{dt}\Big| A_c = 0 = k_2(1-b)\theta + \lambda_c S_c,$$

$$\frac{dI_c}{dt}\Big| I_c = 0 = k_3(1-b)\theta + \sigma_c A_c,$$

$$\frac{dR_c}{dt}\Big| R_c = 0 = \gamma_c I_c,$$

$$\frac{dA_a}{dt}\Big| A_a = 0 = \varepsilon A_c + \lambda_a S_a,$$

$$\frac{dI_a}{dt}\Big| I_a = 0 = \varepsilon I_c + \sigma_a \tau A_a,$$

$$\frac{dR_a}{dt}\Big| R_a = 0 = (1-\sigma_a)\tau A_a + \varepsilon R_c + \gamma_a I_a,$$

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055

$$\frac{dS_v}{dt}\Big| S_v = 0 = \pi_v,$$

$$\frac{dI_v}{dt}\Big| I_v = 0 = \lambda_v S_v.$$

It is clear that these ratios are not negative in the bounding planes of the nonnegative cone $\mathbb{R}^{12}$. Therefore, if we start inside this cone, we will always stay inside this cone in the inward direction of the vector field in all bounding planes. Consequently, all solutions of (2.3)-(2.14) are not negative. For the proof of boundedness, the total population sizes for human and vector are added and we re-write (2.1) and (2.2), i.e.,

$$N_h(t) = V_c(t) + S_c(t) + A_c(t) + I_c(t) + R_c(t) + V_a(t) + S_a(t) + A_a(t) + I_a(t) + R_a(t),$$

$$N_v(t) = S_v(t) + I_v(t).$$

Adding (2.3)-(2.14) for human and vector, we obtain

$$\left.\begin{array}{l} \frac{dN_h}{dt} = b\theta + k_1(1-b)\theta + k_2(1-b)\theta + k_3(1-b)\theta - \mu_h N_h - \delta_c I_c - \delta_a I_a, \\ \frac{dN_v}{dt} = \pi_v - \mu_v N_v - \rho S_v - \rho I_v. \end{array}\right\} \tag{2.15}$$

Suppose $b\theta + k_1(1-b)\theta + k_2(1-b)\theta + k_3(1-b)\theta = w$ then,

$$\left.\begin{array}{l} \frac{dN_h}{dt} \leq w - \mu_h N_h, \\ \frac{dN_v}{dt} \leq \pi_v - \mu_v N_v. \end{array}\right\} \tag{2.16}$$

If we solve (2.16), we find

$$N_h(t) \leq \frac{w}{\mu_h} - \left(\frac{w}{\mu_h} - N_h(t_0)\right) e^{-\mu_h(t-t_0)}$$

and,

$$N_v(t) \leq \frac{\pi_v}{\mu_v} - \left(\frac{\pi_v}{\mu_v} - N_v(t_0)\right) e^{-\mu_v(t-t_0)},$$

where $N_h(t_0)$ and $N_v(t_0)$ are initial conditions. Thus,
$\lim_{t\to\infty} N_h(t) \leq \frac{w}{\mu_h}$ and $\lim_{t\to\infty} N_v(t) \leq \frac{\pi_v}{\mu_v}$,
which shows the conclusion.
From the theorem, we obtain the following region:

$$\Gamma = \Big\{(V_c, V_a, S_c, S_a, A_c, A_a, I_c, I_a, R_c, R_a, S_v, I_v) \in \mathbb{R}^{12} : (V_c, A_c, I_c, S_v) > 0,$$
$$(S_c, V_a, S_a, R_c, A_a, I_a, R_a, I_v) \geq 0; N_h(t) = \frac{w}{\mu_h}; N_v(t) = \frac{\pi_v}{\mu_v}\Big\}$$

which is a positively invariant set for Eqns. (2.3)-(2.14).

3 EQUILIBRIA, REPRODUCTION NUMBER, BIFURCATION AND SENSITIVITY ANALYSES

To obtain malaria information, the model must be studied qualitatively. The equilibria and reproduction number for the model must be derived. Also, the bifurcation and sensitivity of the model's parameters must be examined.

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
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3.1 Equilibria

We begin the analysis by determining the population of individuals in each compartment when the entire human and vector populations are free from malaria. This scenario is termed disease-free equilibrium (DFE) in mathematical epidemiology and it is denoted by
$D^0 = (V_c^0, V_a^0, S_c^0, S_a^0, A_c^0, A_a^0, I_c^0, I_a^0, R_c^0, R_a^0, S_v^0, I_v^0)$ in this analysis. The DFE D^0 is attained when all the infection terms in the model are reduced to zero such that

$$D^0 = \left\{ \frac{b\theta}{\phi_c + \varepsilon + \mu_h}, \frac{\varepsilon V_c^0}{\phi_a + \mu_h}, \frac{k_1(1-b)\theta + \phi_c V_c^0}{\mu_h + \varepsilon}, \frac{\varepsilon S_c^0 + \phi_a}{\mu_h}, 0, 0, 0, 0, 0, 0, \frac{\pi_v}{\mu_v + \rho}, 0 \right\}.$$

When the populations are invaded by malaria, the equilibrium shifts from DFE to the endemic equilibrium denoted by

$$D^* = (V_c^*, V_a^*, S_c^*, S_a^*, A_c^*, A_a^*, I_c^*, I_a^*, R_c^*, R_a^*, S_v^*, I_v^*).$$

Generally, infections transmit into the populations with the emergence of asymptomatic individuals who gradually become visibly infected. Due to the complexity of the model, the existence of the endemic equilibrium D^* shall be established by showing that if the asymptomatic compartments A_c^* and A_a^* are positive (i.e., $A_c^* > 0$ and $A_a^* > 0$) then other infected compartments I_c^* and I_a^* are also positive and the populations are invaded with malaria. Now, solving Eqns. (2.8) and (2.11) in terms of I_c^* and I_a^* then,

$$\left.\begin{aligned} I_c^* &= \tfrac{k_3(1-b)\theta + \sigma_c A_c^*}{\delta_c + \gamma_c + \varepsilon + \mu_h}, \\ I_a^* &= \tfrac{\varepsilon I_c^* + \sigma_a \tau A_a^*}{\delta_a + \gamma_a + \mu_h}. \end{aligned}\right\} \tag{3.1}$$

Since the entire model's variables and parameters are positive, the quantities I_c^* and I_a^* are positive if and only if A_c^* and A_a^* remain positive. Therefore, the endemic equilibrium D^* exists provided that $A_c^* > 0$ and $A_a^* > 0$.

3.2 Reproduction number

The basic reproduction number, conventionally denoted by R_0, is defined by [49] as the average number of secondary infections generated by a typical infectious individual during his or her entire period of infectiousness. The basic reproduction number is an important non-dimensional quantity in epidemiology as it sets the threshold in the study of a disease both for predicting its outbreak and for evaluating its control strategies. Thus, whether a disease becomes persistent or dies out in a community depends on the value of the basic reproduction number R_0. Besides, the basic reproduction number R_0 can be used to analyze the stability of equilibria of epidemic models.
If $R_0 < 1$, it means that every infectious individual produces on average less than one secondary infection and any outbreak in the population is doomed to a rapid failure for the chain of transmission cannot be maintained but if $R_0 > 1$, it means that every infectious individual produces on average more than one secondary infection and the outbreak will take off in the population because the chain of transmission is maintained. A large value for R_0 may indicate the possibility of a major epidemic [34].
The basic idea of the size of the reproduction number as introduced by Sir Ronald Ross is that the value of the reproduction number below unity indicates that the number of infectious individuals and the transmission potential of a disease in a population are insignificant to trigger epidemic in the population whereas the value of the reproduction number above unity implies that the number of infectious individuals and the transmission potential of a disease in a population are enough to

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055

result in the outbreak of the disease in the population. So, the reproduction number is the quantity that governed the spread of a disease in a population.
On the other hand, all control measures of a disease are effective if the value of R_e, the effective reproduction number, is less than one. The effective reproduction number, R_e measures the average number of new infections generated by a typical infectious individual in a community where intervention strategies are on ground. Hence, the computation of the reproduction number is central to the analysis of any epidemic model in order to be able to predict whether an epidemic will take off or not in a population. In this analysis, the next generation matrix approach formulated by [49] but subsequently developed by [51], which has been used in numerous epidemic models, [12, 32, 33, 34, 38], shall be employed to compute the reproduction numbers of the present model. Because infection can spread from both infectious humans and vectors, R_0 in the present analysis is made up of two parts as in other age-structured malaria models [12, 32, 33, 34]. It is made up of R_h and R_d; the infection transmission potentials from infectious mosquitoes to susceptible children and adults and from infectious children and adults to susceptible mosquitoes respectively which are derived from the compartments A_c, A_a, I_c, I_a and I_v following the approach in [50]) outlined as follows

$$\mathcal{F}=\begin{pmatrix} \frac{n(1-m)\beta_c I_v {S_c}^0}{I_v+\vartheta} \\ \frac{n\beta_a I_v {S_a}^0}{I_v+\vartheta} \\ 0 \\ 0 \\ \frac{n\beta_v[\eta(A_c+A_a)+I_c+I_a]{S_c}^0}{(A_c+A_a+I_c+I_a)+\varphi} \end{pmatrix} \text{ and } \mathcal{V}=\begin{pmatrix} (\sigma_c+\varepsilon+\mu_h)A_c \\ -\varepsilon A_c+(\tau+\mu_h)A_a \\ -\sigma_c A_c+(\delta_c+\gamma_c+\mu_h)I_c \\ -\varepsilon I_c-\sigma_a\tau A_a+(\delta_a+\gamma_a+\mu_h)I_a \\ \mu_v+\rho \end{pmatrix}.$$

Therefore,

$$F=\begin{pmatrix} 0 & 0 & 0 & 0 & \frac{n(1-m)\beta_c {S_c}^0}{\vartheta} \\ 0 & 0 & 0 & 0 & \frac{n\beta_a {S_a}^0}{\vartheta} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{n\eta\beta_v {S_v}^0}{\varphi} & \frac{n\eta\beta_v {S_v}^0}{\varphi} & \frac{n\beta_v {S_v}^0}{\varphi} & \frac{n\beta_v {S_v}^0}{\varphi} & 0 \end{pmatrix},$$

$$V=\begin{pmatrix} (\sigma_c+\varepsilon+\mu_h) & 0 & 0 & 0 & \frac{n(1-m)\beta_c {S_c}^0}{\vartheta} \\ -\varepsilon & (\tau+\mu_h) & 0 & 0 & 0 \\ -\sigma_c & 0 & (\delta_c+\gamma_c+\varepsilon+\mu_h) & 0 & 0 \\ 0 & -\sigma_a\tau & -\varepsilon & (\delta_a+\gamma_a+\mu_h) & 0 \\ 0 & 0 & 0 & 0 & \mu_v+\rho \end{pmatrix}$$

and,

$$V^{-1}=\begin{pmatrix} \frac{1}{q_1} & 0 & 0 & 0 & 0 \\ \frac{\varepsilon}{q_1 q_2} & \frac{1}{q_2} & 0 & 0 & 0 \\ \frac{q_3}{q_1 q_2} & 0 & \frac{1}{q_4} & 0 & 0 \\ \frac{\varepsilon(q_2 q_3+q_4 q_5)}{q_1 q_2 q_4 q_6} & \frac{q_5}{q_2 q_6} & \frac{\varepsilon}{q_4 q_6} & \frac{1}{q_6} & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{q_7} \end{pmatrix},$$

where

$$q_1=\sigma_a+\varepsilon+\mu_h, q_2=\tau+\mu_h, q_3=\sigma_c, q_4=\delta_c+\gamma_c+\varepsilon+\mu_h, q_5=\sigma_a\tau,$$
$$q_6=\delta_a+\gamma_a+\mu_h, q_7=\mu_v+\rho.$$

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055

The reproduction number (R_0) represents the dominant eigenvalue of the generation matrix FV^{-1} which works to be

$$R_0 = \sqrt{\frac{n(1-m)\beta_c S_c^0}{\vartheta q_7}\left[\frac{\eta n\beta_v S_v^0}{q_1\varphi} + \frac{n\beta_v q_3 S_v^0}{q_1 q_2\varphi}\right] + \frac{n\beta_a S_a^0}{\vartheta q_7}\left[\frac{\eta\varepsilon n\beta_v S_v^0}{q_1 q_2\varphi} + \frac{\eta\varepsilon\beta_v S_v^0}{q_1 q_2 q_4 q_6\varphi}\right]} \tag{3.2}$$

In (3.2), while $\frac{n(1-m)\beta_c S_c^0}{\vartheta q_7}\left[\frac{\eta n\beta_v S_v^0}{q_1\varphi} + \frac{n\beta_v q_3 S_v^0}{q_1 q_2\varphi}\right]$ quantifies the spread of malaria from infectious vectors to susceptible children and from infectious children to susceptible vectors, $\frac{n\beta_a S_a^0}{\vartheta q_7}\left[\frac{\eta\varepsilon n\beta_v S_v^0}{q_1 q_2\varphi} + \frac{\eta\varepsilon\beta_v S_v^0}{q_1 q_2 q_4 q_6\varphi}\right]$ quantifies the spread of malaria from infectious vectors to susceptible adults and from infectious adults to susceptible vectors. Substituting the values of S_c^0, S_a^0 and S_v^0 into (3.2), we have

$$\begin{aligned}\mathcal{R}_0 = {} & \frac{n^2(1-m)\beta_c\left\{q_1 q_8 k_1\left(1-b\right)\theta + \phi_c b\right\}}{\vartheta q_7 q_8 q_9}\left[\frac{\pi_v\eta\beta_v}{(\mu_v+\rho)q_1\varphi} + \frac{\pi_v\beta_v q_3}{(\mu_v+\rho)q_1 q_2\varphi}\right] \\ & + \frac{n^2\varepsilon\beta_a}{\vartheta q_7}\left\{\frac{\varepsilon\left[q_1 q_8 k_1\left(1-b\right)\theta + \phi_c b\right] + \phi_a}{\mu_h q_8 q_9}\right\}\left[\frac{\pi_v\eta\beta_v}{(\mu_v+\rho)q_1 q_2\varphi} + \frac{\pi_v\beta_v}{(\mu_v+\rho)q_1 q_2 q_4 q_6\varphi}\right],\end{aligned} \tag{3.3}$$

The reproduction number in (3.3) reveals the importance of vaccines in the control and eradication of malaria through the vaccination parameter m, vaccination rate of susceptible children. If the coverage and efficacy of the vaccines are high so that $m \to 1$ then malaria transmission could be greatly reduced particularly from the children who are more vulnerable to the disease. Therefore, the development of malaria vaccines is a renewed hope to mankind. The vaccines can prevent malaria spread and minimize malaria mortality with high coverage and efficacy.

3.3 Bifurcation analysis

Mathematical models present a comparatively inexpensive means to investigate the spread and control of diseases [51]. Once a mathematical model is developed, the prospect of the disease can be revealed by the parameters of the model when the important non-dimensional epidemiological quantity known as the basic reproduction number is computed. The computed reproduction number can be employed to perform bifurcation and sensitivity analyses to reveal the prospect of the disease. So whether data are available or not, mathematical models, through bifurcation and sensitivity analyses, can guide the policy makers towards the achievement of their objectives. The main concern of epidemiologists is to establish a condition under which a disease can be eradicated from a population [52]. This condition is governed by the size of the basic reproduction number which is defined by [49] as the average number of secondary infections caused by an infectious individual during his or her entire period of infectiousness. However, contrary to the analysis of the basic reproduction number, there may not be a total elimination of a disease in a population even if the reproduction number is less than unity. The bedrock of this idea is bifurcation theory whose earliest work is attributable to the French mathematician Henri Poincare (1854 – 1912) [53].
Bifurcation is the study of changes in the qualitative or topological structure of dynamical system. It occurs when a small smooth change to a parameter (bifurcation parameter) of a system of differential equation causes a sudden qualitative or topological change in the behavior of the system. In epidemiology, bifurcation is a phenomenon which shows how the equilibrium of an epidemic model divides into a branch at the bifurcation point (i.e. $R_0 = 1$) thereby, resulting into changes in the

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055

stability and qualitative behavior of the model. Bifurcation provides a way to understand changes in the stability properties of epidemic models as some parameters of the models vary.
Researchers have identified forward and backward bifurcations in the analysis of disease transmission models. A forward bifurcation occurs in a disease model if a stable disease-free equilibrium of the model losses its stability and becomes a stable endemic equilibrium as the reproduction number R_0 of the model takes off through one. The existence of forward bifurcation does not have a major health implication as the basic requirement $R_0 < 1$ remains the necessary and sufficient condition for disease eradication. On the other hand, numerous studies have shown that the classical requirement of the basic reproduction number R_0 being less than unity is just a necessary condition for community wide eradication of a disease but not sufficient [54, 55, 56].
These studies have verified this fact by exploring the phenomenon of bistability, where multiple stable equilibria co-exist, in some epidemic models. These models, in general, undergo backward bifurcations which are sufficient for the existence of stable endemic equilibria when $R_0 < 1$. In other words, these studies have shown that a stable endemic equilibrium can co-exist with a stable disease-free equilibrium at the bifurcation point. Thus, unlike in many classical disease transmission models, reducing R_0 to values less than unity does not guarantee the community-wide eradication of a disease [57, 58, 59]. This means that the occurrence of a backward bifurcation may have serious public health implications in the control or eradication of an epidemic since the condition $R_0 < 1$ is not sufficient for disease eradication.
The existence of backward bifurcation shall be studied for the model following the center manifold theory introduced by [60] which has been employed in many epidemic models [54, 55, 56]. To apply the theorem, the variables of the model are transformed in such a way that $x_1 = V_c$, $x_2 = V_a$, $x_3 = S_c$, $x_4 = S_a$, $x_5 = A_c$, $x_6 = A_a$, $x_7 = I_c$, $x_8 = I_a$, $x_9 = R_c$, $x_{10} = R_a$, $x_{11} = S_v$, $x_{12} = I_v$.
If $\boldsymbol{X} = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10}, x_{11}, x_{12})^T$, the system of equations (2.3)-(2.14) becomes $\frac{dX}{dt} = F(\boldsymbol{X})$ where $F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10}, f_{11}, f_{12})$. Thus, the model Eqs. (2.3)-(2.14) are transformed to

$$\frac{dx_1}{dt} = b\theta - (\phi_c + \varepsilon + \mu_h)\, x_1, \tag{3.4}$$

$$\frac{dx_2}{dt} = \varepsilon x_1 - (\mu_h + \phi_a)\, x_2, \tag{3.5}$$

$$\frac{dx_3}{dt} = k_1\,(1-b)\,\theta + \phi_c x_1 + \psi_c x_9 - \lambda_c x_3 - (\mu_h + \varepsilon)\, x_3, \tag{3.6}$$

$$\frac{dx_4}{dt} = \varepsilon x_3 + \phi_a x_2 + \psi_a x_{10} - \lambda_a x_4 - \mu_h x_4, \tag{3.7}$$

$$\frac{dx_5}{dt} = k_2\,(1-b)\,\theta + \lambda_c x_3 - (\sigma_c + \varepsilon + \mu_h)\, x_5, \tag{3.8}$$

$$\frac{dx_6}{dt} = \varepsilon x_5 + \lambda_a x_4 - (\tau + \mu_h)\, x_6 \tag{3.9}$$

$$\frac{dx_7}{dt} = k_3\,(1-b)\,\theta + \sigma_c x_5 - (\delta_c + \gamma_c + \varepsilon + \mu_h)\, x_7 \tag{3.10}$$

$$\frac{dx_8}{dt} = \varepsilon x_7 + \sigma_a \tau x_6 - (\delta_a + \gamma_a + \mu_h)\, x_8 \tag{3.11}$$

$$\frac{dx_9}{dt} = \gamma_c x_7 - (\psi_c + \varepsilon + \mu_h)\, x_9, \tag{3.12}$$

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055

$$\frac{dx_{10}}{dt} = (1-\sigma_a)\tau x_6 + \varepsilon x_9 + \gamma_a x_8 - (\psi_a + \mu_h)x_{10}, \tag{3.13}$$

$$\frac{dx_{11}}{dt} = \pi_v - \lambda_v x_{11} - (\mu_v + \rho)x_{11}, \tag{3.14}$$

$$\frac{dx_{12}}{dt} = \lambda_v x_{11} - (\mu_v + \rho)x_{12}, \tag{3.15}$$

Since the infection of more and more children with malaria can escalate malaria transmissions in both human and vector populations and aggravate malaria deaths in humans, we assume a bifurcation point and choose β_v, probability of infection of susceptible vectors per bite of the infected host as the bifurcation parameter at the bifurcation point $R_0 = 1$. We wish to investigate whether perturbations in β_v would instigate backward bifurcation or not at the bifurcation point. The parameter β_v is perturbed so that β_v changes β_v^* and the variational matrix of the system (3.4)-(3.15) around the disease-free equilibrium D^0 is computed as follows

$$J(D^0)\big|_{\beta_v=\beta_{v^*}} =$$

$$\begin{pmatrix}
-q_8 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\varepsilon & -q_{10} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\phi_c & 0 & -q_9 & 0 & 0 & 0 & 0 & 0 & \psi & 0 & 0 & \frac{-n(1-m)\beta_c {S_c}^0}{\vartheta} \\
0 & \phi_a & \varepsilon & -\mu_h & 0 & 0 & 0 & 0 & 0 & \psi & 0 & \frac{-n\beta_a {S_a}^0}{\vartheta} \\
0 & 0 & 0 & 0 & -q_{11} & 0 & 0 & 0 & 0 & 0 & 0 & \frac{n(1-m)\beta_c {S_c}^0}{\vartheta} \\
0 & 0 & 0 & 0 & \varepsilon & -q_2 & 0 & 0 & 0 & 0 & 0 & \frac{n\beta_a {S_a}^0}{\vartheta} \\
0 & 0 & 0 & 0 & q_3 & 0 & -q_4 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \sigma_a\tau & \varepsilon & -q_6 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \gamma_c & 0 & -q_{12} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & (1-\sigma_a)\tau & 0 & \gamma_a & \varepsilon & -q_{13} & 0 & 0 \\
0 & 0 & 0 & 0 & -\eta q_{14} & -\eta q_{14} & -q_{14} & -q_{14} & 0 & 0 & -q_7 & 0 \\
0 & 0 & 0 & 0 & \eta q_{14} & \eta q_{14} & q_{14} & q_{14} & 0 & 0 & 0 & -q_7
\end{pmatrix}$$

where

$$q_{10} = \mu_h + \phi_a, q_{11} = \sigma_c + \varepsilon + \mu_h, q_{12} = \psi_c + \varepsilon + \mu_h, q_{13} = \psi_a + \mu_h, q_{14} = \frac{n\beta_v^* S_v}{\varphi}.$$

The associated right eigenvectors of $J(D^0)|_{\beta_v=\beta_v^*}$ that are represented by $w = (w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10}, w_{11}, w_{12})^{\mathcal{T}}$ can be obtained and are given in Eqns. (3.16)-(3.27),

$$-q_8 w_1 = 0, \tag{3.16}$$

$$\varepsilon w_1 - q_{10} w_2 = 0, \tag{3.17}$$

$$\phi_c w_1 - q_9 w_3 + \psi w_9 - \frac{n(1-m)\beta_c S_c^0}{\vartheta} w_{12} = 0, \tag{3.18}$$

$$\phi_a w_2 + \varepsilon w_3 - \mu_h w_4 + \psi w_{10} - \frac{n\beta_a S_a^0}{\vartheta} w_{12} = 0, \tag{3.19}$$

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055

$$-q_{11}w_5 + \frac{n(1-m)\beta_c S_c^0}{\vartheta} w_{12} = 0, \tag{3.20}$$

$$\varepsilon w_5 - q_2 w_6 + \frac{n\beta_a S_a^0}{\vartheta} w_{12} = 0, \tag{3.21}$$

$$q_3 w_5 - q_4 w_7 = 0, \tag{3.22}$$

$$\sigma_a \tau w_6 + \varepsilon w_7 - q_6 w_8 = 0, \tag{3.23}$$

$$\gamma_c w_7 - q_{12} w_9 = 0, \tag{3.24}$$

$$(1-\sigma_a)\tau w_6 + \gamma_a w_8 + \varepsilon w_9 - q_{13} w_{10} = 0, \tag{3.25}$$

$$-\eta q_{14} w_5 - n q_{14} w_6 - q_{14} w_7 - q_{14} w_8 - q_7 w_{11} = 0, \tag{3.26}$$

$$\eta q_{14} w_5 + n q_{14} w_6 + q_{14} w_7 + q_{14} w_8 - q_7 w_{12} = 0. \tag{3.27}$$

Solving (3.16)-(3.27),

$$w_1 = \frac{q_{10}}{\varepsilon} w_2 > 0, \tag{3.28}$$

$$w_2 = w_2 > 0, \tag{3.29}$$

$$w_3 = \frac{1}{q_3}\left\{\frac{\phi_c q_{10}}{\varepsilon} w_2 + \frac{\psi q_{12}}{\gamma_c} w_7 - \frac{n(1-m)\beta_c}{\vartheta} w_{12}\right\}, \tag{3.30}$$

$$\begin{aligned} w_4 = \frac{1}{\mu_h}\Bigg\{ & \left(\phi_a + \frac{\varepsilon\phi_c q_{10}}{q_9}\right) w_2 + \left(\frac{\varepsilon\psi q_{12}}{q_9\gamma_c} + \frac{\psi}{q_{13}}\left(\frac{\gamma_a}{q_6} + \frac{\varepsilon q_{12}}{\gamma_c}\right)\right) w_7 \\ & - \left(\frac{q_{15}}{\vartheta q_9} + \frac{n\beta_a S_a^0}{\vartheta} - \frac{\psi}{q_{13}}\left[\frac{(1-\sigma_a)\tau}{q_2}\left(\frac{\varepsilon q_{15}}{\vartheta q_{11}} + \frac{n\beta_a S_a^0}{\vartheta}\right)\right] - \frac{\gamma_a}{q_6}\left(\frac{\sigma_a\tau q_{15}}{\vartheta q_{11}} + \frac{n\beta_a S_a^0}{\vartheta}\right)\right) w_{12}\Bigg\}, \end{aligned} \tag{3.31}$$

$$w_5 = \frac{1}{q_{11}}\left\{\frac{n(1-m)\beta_c S_c^0}{\vartheta}\right\} w_{12} > 0, \tag{3.32}$$

$$w_6 = \frac{1}{q_2}\left\{\frac{\varepsilon n(1-m)\beta_c S_c^0}{\vartheta q_{11}} + \frac{n\beta_a S_a^0}{\vartheta}\right\} w_{12} > 0, \tag{3.33}$$

$$w_7 = w_7 > 0, \tag{3.34}$$

$$w_8 = \frac{1}{q_6}\left\{\left[\frac{\sigma_a\tau n(1-m)\beta_c S_c^0}{\vartheta q_{12}} + \frac{n\beta_a S_a^0}{\vartheta}\right] w_{12} + w_7\right\} > 0, \tag{3.35}$$

$$w_9 = \frac{q_{12}}{\gamma_c} w_7 > 0, \tag{3.36}$$

$$w_{10} = \frac{1}{q_{13}}\left\{\left[\frac{(1-\sigma_a)\tau}{q_2}\left(\frac{\varepsilon q_{15}}{\vartheta q_{11}} + \frac{n\beta_a S_a^0}{\vartheta}\right) + \frac{\gamma_a}{q_6}\left(\frac{\sigma_a\tau q_{15}}{\vartheta q_{12}} + \frac{n\beta_a S_a^0}{\vartheta}\right)\right] w_{12} + \left(\frac{\gamma_a}{q_6} + \frac{\varepsilon q_{12}}{\gamma_c}\right) w_7\right\} > 0, \tag{3.37}$$

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055

$$w_{11} = w_{11} > 0, \tag{3.38}$$

$$w_{12} = w_{12} > 0. \tag{3.39}$$

Likewise, the left eigenvectors of the transformed model represented by $v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}, v_{11}, v_{12})^{\mathcal{T}}$ can be derived and are stated as follows. $v_1 = v_2 = v_3 = v_4 = v_9 = v_{10} = 0$ but $v_5 = v_5 > 0$, $v_6 = v_6 > 0$, $v_7 = v_7 > 0$, $v_8 = v_8 > 0$, $v_{11} = v_{11} > 0$ and $v_{12} = v_{12} > 0$. Now, the task is to derive the bifurcation coefficients a and b, the procedure of which is described in Theorem 4.1 in [60]. As specified in Theorem 4.1 in [60], the model undergoes backward bifurcation if a and b are both positive. The existence of a backward bifurcation necessitates a simultaneous coexistence of a stable non-trivial equilibrium with stable disease eradication equilibrium.

Computation of a: Following the procedure in Theorem 4.1 in [60], we employ the formula

$$a = \sum_{k,i,j=1}^{12} v_k w_i w_j \frac{\partial^2}{\partial x_i \partial x_j} f_k(0,0),$$

with $f_k = f_{12} = \frac{n\beta_v^*[\eta(x_5+x_6)+x_7+x_8]}{(x_5+x_6+x_7+x_8)+\varphi} x_{11} - q_7 x_{12}$ so that

$$a = \frac{2}{\varphi} v_{12} w_5 w_{11} n\eta\beta_v^* + \frac{2}{\varphi} v_{12} w_6 w_{11} n\eta\beta_v^* + \frac{2}{\varphi} v_{12} w_7 w_{11} n\beta_v^* + \frac{2}{\varphi} v_{12} w_8 w_{11} n\beta_v^* \tag{3.40}$$

Substituting the values of w_5, w_6 and w_8 in (3.28-3.39) into (3.40) noting that $v_{12} > 0$, $w_7 > 0$, $w_{11} > 0$ and $w_{12} > 0$ then,

$$\begin{aligned} a = {} & \frac{2}{\varphi} v_{12} \left\{ \frac{n(1-m)\beta_c S_c^0}{q_{11}\vartheta} \right\} w_{12} w_{11} n\eta\beta_v^* \\ & + \frac{2}{\varphi} v_{12} \left\{ \frac{\varepsilon n(1-m)\beta_c S_c^0}{\vartheta q_2 q_{11}} + \frac{n\beta_a S_a^0}{\vartheta q_2} \right\} w_{12} w_{11} n\eta\beta_v^* \\ & + \frac{2}{\varphi} v_{12} w_7 w_{11} n\beta_v^* \\ & + \frac{2}{\varphi} v_{12} \frac{1}{q_6} \left\{ \left[\frac{\sigma_a \tau n(1-m)\beta_c S_c^0}{\vartheta q_{12}} + \frac{n\beta_a S_a^0}{\vartheta} \right] w_{12} + w_7 \right\} w_{11} n\beta_v^* \end{aligned} \tag{3.41}$$

Computation of b: Following the same procedure

$$b = \sum_{k,i,j=1}^{12} v_k w_i \frac{\partial^2}{\partial x_i \partial \beta_v^*} f_k(0,0)$$

$$\Rightarrow \; b = \frac{2n}{\varphi} v_{12} w_{12} \left(1+\eta\right) S_v^0 > 0. \tag{3.42}$$

Since the model monitors human and animal populations, all the variables and parameters are positive. Following [60], the model exhibits backward bifurcation if a and b are positive. According to [60], b is always positive, the condition which has already been met given the value of b in (3.42). Therefore, the malaria model undergoes backward bifurcation since a is also positive in (3.41). The results of bifurcation analysis have revealed some important factors that can frustrate malaria elimination. It has been revealed in (3.41) that the existence of vector parameter (i.e., β_v^*) in human

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055

population can enhance malaria permanence for as long as $\beta_v^* > 0$. However, the eradication of malaria is possible if one of φ, the rate of effectiveness of malaria prevention/treatment or ϑ, the rate of control of vectors or both are intensified. It is evident from (3.41) that $a = 0$ if $\varphi \to \infty$ or $\vartheta \to \infty$ or if both $\varphi \to \infty$ and $\vartheta \to \infty$. Under this condition (i.e., $a = 0$) and backward bifurcation is avoided.

The results have important implications for malaria management and control and can guide the policy makers. First, the development of malaria vaccines and the subsequent approval of its use in some malaria endemic regions (e.g. Ghana, Nigeria, etc.) are a welcome development. However, while the vaccines may guarantee the necessary protection (φ), its application and coverage to the fullest may not instigate malaria eradication. It is evident from (3.41) that if m, the rate of application of vaccines to the susceptible children, is equal to one, $a \neq 0$ but $a > 0$. Therefore, the prevalence of vectors in the endemic regions necessitates adequate vector control (ϑ) in addition to the application of vaccines. Both parameters, φ and ϑ, have to be integrated into the policy designed to eradicate malaria. Besides, the two parameters have to be taken with all seriousness in the control of malaria.

4 Simulation and Discussion

The simulations are aided by the computer-in-built Runge-Kutta package implemented in software Maple and the parameter values adopted for simulation, which are from the related literature as well as assumptions, are displayed in Table 3. The definitions of the parameters are in Table 2.

Table 3: Values and Sources for the model parameters

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055

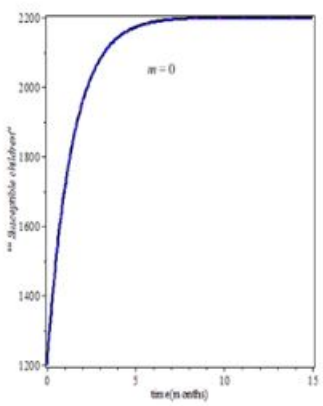
Parameters	Values	Sources
μ_h	0.01 day^{-1}	[61]
δ_c	0.0005 day^{-1}	[61]
δ_a	0.0002 day^{-1}	[61]
θ	0.25	Assumed
π_v	0.85 day^{-1}	Assumed
μ_v	0.05 day^{-1}	[62]
ρ	0.025 day^{-1}	Assumed
β_c	0.75 day^{-1}	[61]
β_a	0.27 day^{-1}	[61]
β_v	0.00064 day^{-1}	Assumed
n	0.0005 day^{-1}	Assumed
m	0.4 day^{-1}	Assumed
ϕ_c	0.7 day^{-1}	Assumed
ϕ_a	0.005 day^{-1}	Assumed
ε	0.183 day^{-1}	[61]
ψ_c	0.01 day^{-1}	[61]
ψ_a	0.0027 day^{-1}	[61]
b	0.1 day^{-1}	Assumed
σ_c	0.1 day^{-1}	[61]
σ_a	0.2 day^{-1}	[61]
η	0.05	Assumed
γ_c	0.014 day^{-1}	[63]
γ_a	0.002 day^{-1}	[64]
τ	0.02	Assumed
ϑ	0.75	[65]
φ	0.75	[66]
m	0.4	[67]
k_1	0.55	Assumed
k_2	0.15	Assumed
k_3	0.01	Assumed

Given Table 3, plots are generated in Figure 2 to Figure 3 to visualize the effects of vaccination parameter (m) on the dynamics of malaria in children.

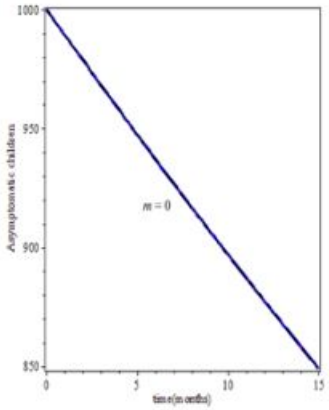
With parameter values in Table 3, we are able to generate plots in Figure 2 and we can visualize the effect of vaccination on the dynamics of malaria particularly at various stages of infections for children. We place emphasis on children because malaria has more adverse effects on children especially those who are below five years of age [14]. It can be observed at a glance from Figure 2 that the absence vaccine complicates susceptibility and infectivity of malaria in children. This is because the populations of susceptible and infectious children in (a) and (c) in Figure 2 rise continuously. The fall in the population of asymptomatic children in (b) indicates an instant progression from the asymptomatic stage of infection to full infectious stage. Therefore, vaccination can play a major role in preventing malaria infection and in reducing the escalation of the disease in children.

IJMSO

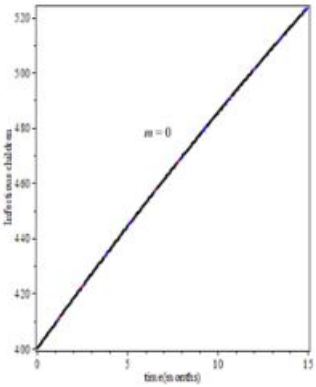
International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055



(a) Effect of absence of vaccine on the population of susceptible children.

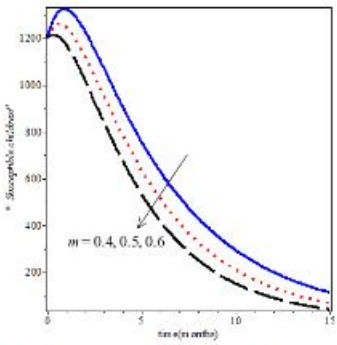


(b) Effect of absence of vaccine on the population of asymptomatic children.

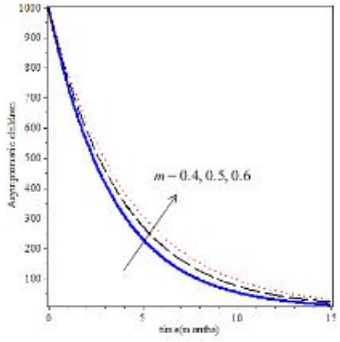


(c) Effect of absence of vaccine on the population of infectious children.

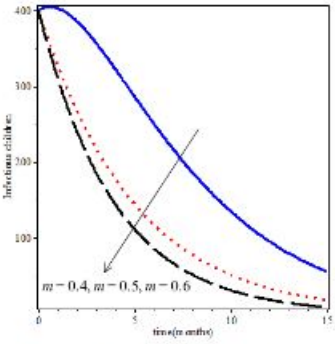
Figure 2: Simulation showing the effect of no vaccine on the dynamics of malaria in children



(a) Effect of vaccine on the population of susceptible children.



(b) Effect of vaccine on the population of asymptomatic children.



(c) Effect of vaccine on the population of infectious children.

Figure 3: Simulation showing the effect of decrease in vector population on the changes in the epidemiological status of children

In Figure 3, an increase in the vaccination parameter (m) from 0.4 through to 0.6 is accompanied with simultaneously reductions in the populations of susceptible and infectious children as indicated by the arrows in (a) and (c) in Figure 3. Although, there is an increase in the population of asymptomatic children in (b), only few of them progress to the infectious stage. The effectiveness and coverage of vaccination is able to bring down the population of the asymptomatic children. It

IJMSO

International Journal of Mathematical Sciences and Optimization: Theory and Applications
10(3), 2024, Pages 106 - 132
https://doi.org/10.5281/zenodo.13626055

is therefore evident from Figure 3 that the development of malaria vaccine is a plus to the struggle against malaria eradication.

5 Conclusion

Malaria is a disease that can spread from humans to vectors and from vectors to humans and has serious health and economic implications. In this study, a mathematical analysis of the dynamics of malaria spread in human and vector populations has been presented. Because of the recent development of malaria vaccine and the subsequent approval of its use in some malaria endemic regions to combat malaria, an age-structured mathematical model has been developed to investigate various factors (e.g. asymptomatic carriers, relapse, migration, etc.) that could limit the success of vaccine applications in malaria control. Malaria dynamics has been examined with a focus on the conditions that can frustrate the eradication of the disease (bifurcation analysis) Overall, the findings from the study give a better understanding of malaria dynamics with respect to vaccine development and vaccine approval to combat malaria. It can be observed from the expression for R_0 that malaria spread is influenced by the recruitment parameter for vectors π_v as well as the transmission parameters β_v, β_c and β_a. For example, when all the stated parameters rise while other parameters are held constant, R_0 increases and this has negative control effects on malaria. The simulations have been run to display the behaviors of the disease and it has been revealed that malaria eradication, through vaccine development and vaccine approval to control the disease even with high coverage of vaccine applications, might remain a tall dream.
The bifurcation analysis shows that factors such as migration, relapse, asymptomatic carriers, etc, that could influence vector population particularly the population of infectious vectors, can shape malaria dynamics. Malaria dynamics could be seriously influenced and it is evident from the expression for the bifurcation coefficient "a" that the application of vaccination parameter m, even to the fullest, may not remove malaria endemicity. Therefore, effective vector control (ϑ), efficient malaria prevention/treatment (φ) and adequate testing of the new arrivals which will improve isolation are required in addition to the application of vaccines to overcome malaria.

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