Modelling the Impact of Misdiagnosis and Treatment on the Dynamics of Malaria Concurrent and Co-infection with Pneumonia

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Abstract

Incidences of misdiagnosis of diseases with similar symptoms as malaria has increased lately due to the increasing levels of endemicity of these diseases and their co-infection with malaria. In this paper a mathematical model for the impact of misdiagnosis and treatment of pneumonia as malaria has been developed and analyzed. The dynamics
of misdiagnosis is compared with that of accurate diagnosis and prompt and correct treatment. We establish the existence of local asymptotic stability of the disease-free equilibrium when $R_{MP} < 1$. The results show that the disease-free equilibrium may not be globally asymptotically stable whenever $R_{MP} < 1$. The existence of backward bifurcation has been shown using the Lyapunov second method. We deduce that in a situation of prompt pneumonia treatment there exists a unique endemic equilibrium which is globally asymptotically stable.

Mathematics Subject Classification: 35E21

Keywords: Similar symptoms, Misdiagnosis, Stability, Backward bifurcation

1 Introduction

Infectious diseases are the most prevalent and the main cause of ill health and death in the world and their impact is most felt among the poorest who have least physical and financial resources and limited or no access to integrated health care, prevention tools and medication. Malaria and pneumonia are the leading causes of death among the poor in developing countries [13]. In Kenya where malaria and pneumonia are endemic, it is common for people to be infected by either or both. Malaria and pneumonia always present similarly and the two diseases are always confused. More often than not a patient presenting with fever, headache and muscle pains is given anti-malarials without ascertaining the exact cause of those symptoms, and those infected with both pneumonia and malaria often have symptom overlap which would otherwise necessitate dual treatment with both anti-malarials and antibiotics if proper tests were done. However interventions usually target single disease, malaria, this leads to mistreatment with anti-malaria and delays in seeking care for the pneumonia, thus risking increased incidences of pneumonia.

The diagnosis approaches currently used may not allow correct diagnosis [8]. Clinical diagnosis the most widely used is unreliable and there is always delays in establishing the correct diagnosis which result in high morbidity and mortality due to pneumonia.

Many models on common infectious diseases and co-infection have been developed [6], but none has been developed on the misdiagnosis of pneumonia as malaria. Yet because of the similarity of the symptoms leading to the misdiagnosis of pneumonia, pneumonia is a major killer in this combination. In this study we have developed a mathematical model for the dynamics of misdiagnosis of pneumonia as malaria in malaria-pneumonia concurrent and co-infection. The mathematical model can help in building a positive perspective towards the use of diagnostic tests before prescription and dispensing of anti-malarials.
2 Model Description and Formulation

The model subdivides the total human population $N_H$ and the total vector population $N_V$ into various components depending on their disease status. At time $t$ there are $S_H$ and $S_V$ susceptible humans and mosquitoes respectively. $I_M$, $I_P$ and $I_{MP}$ are the densities of human infectives with malaria, pneumonia and dually infected with malaria and pneumonia, $I_V$ are the infectious mosquitoes and $I^d$ are the individuals with pneumonia but misdiagnosed and untreated. The model assumes no partial recovery for both diseases in human and mosquito. $N_H = S_H + I_M + I_{MP} + I^d + I_P$ and $N_H = S_V + I_V$ are respectively the total human and vector populations at time $t$. The constant per capita recruitment rate into susceptible humans and mosquito are $\Lambda_H$ and $\Lambda_V$ correspondingly. Susceptible humans become infectious with malaria and pneumonia at rates $\lambda_M$ and $\lambda_P$ respectively, while mosquitoes become infectious at rate $\lambda_V$. Individuals in the human population experience per capita natural death rate of $\mu_H$ and similarly the mosquito per capita natural death rate is $\mu_V$. Let $a$ be the per capita biting rate of mosquito, then there are $\frac{aN_V}{N_H}$ bites per human per time, the proportion of the total number of bites that is infectious to humans is $\frac{I_V}{N_V}$, the number of potentially infectious bites to susceptible humans per time is $aI_VS_HN_H$. However the probability that a bite by an infected mosquito on a susceptible human will transfer the infection to human is $c$, thus susceptible humans acquire malaria at a rate

$$\lambda_M = \frac{acI_V}{N_H} \tag{1}$$

Similarly susceptible individuals acquire pneumonia infection at the rate

$$\lambda_P = \frac{\beta(I_P + \psi(I^d) + \sigma(I_{MP}))}{N_H} \tag{2}$$

where $\beta$ is the effective contact rate associated with pneumonia infection and the modification parameter $\psi$ accounts for the risk of infectiousness of individuals in $I^d$ while $\sigma$ accounts for very high infectiousness in the double infected individuals $I_{MP}$ whose pneumonia has been misdiagnosed. We define the force of infection of susceptible mosquito by infected human as

$$\lambda_V = \frac{\vartheta a(I_M + \pi I_{MP})}{N_H} \tag{3}$$

where $\vartheta$ is the transmission probability for mosquito infection, $a$ is the biting rate of mosquitoes, $\pi$ is modification parameter accounting for increased likelihood of infection of vectors by the highly infectious dually infected individuals. Malaria infectious humans recover with a rate of $q$ (without regaining immunity) to join the susceptible class. Humans with pneumonia are misdiagnosed
and progress to $I^d$ class at rate $\rho$. All malaria only infected individuals $I_M$ or pneumonia $I_P$ only infected individuals suffer disease induced death at the rate $\delta_M, \delta_P$ respectively, however those in $I^d$ class suffer disease induced death at rate $\varpi \delta_P$ where $\varpi$ accounts for increased mortality due to prolonged time taken without the right diagnosis and treatment. Individuals in $I^d$ class acquire malaria infection at a rate $\gamma \lambda_M$ where the parameter $\gamma$ accounts for increased rate of acquiring malaria due to the very low immunity caused by prolonged stay with pneumonia. When pneumonia is misdiagnosed as malaria, the patient is given anti-malaria, pneumonia continues eating and the body defense system weakens and leads to death. In case the person gets malaria infection also, the body weakens faster and kills faster. Hence individuals in $I_{MP}$ class suffer disease induced death at rate $\theta \delta_{MP}$, where $\theta$ accounts for accelerated deaths by malaria and pneumonia together. We assume that individuals in $I_M$ class are treated with anti-malaria and do not get double infected with pneumonia. From the above definitions and explanations we have the following model of malaria and pneumonia concurrent and co-infection.

\[
\begin{align*}
\frac{dS_H}{dt} &= \Lambda_H - \lambda_M S_H - \lambda_P S_H - \mu_H S_H + q I_M \\
\frac{dI_M}{dt} &= \lambda_M S_H - \delta_M I_M - \mu_H I_M - q I_M \\
\frac{dI_P}{dt} &= \lambda_P S_H - \rho I_P - \delta_P I_P - \mu_H I_P \\
\frac{dI^d}{dt} &= \rho I_P + \xi I_{MP} - \gamma \lambda_M I^d - \varpi \delta_P I^d - \mu_H I^d \\
\frac{dI_{MP}}{dt} &= \gamma \lambda_M I^d - \xi I_{MP} - \theta \delta_{MP} I_{MP} - \mu_H I_{MP} \\
\frac{dS_V}{dt} &= \Lambda_V - \mu_V S_V - \lambda_V S_V \\
\frac{dI_V}{dt} &= \lambda_V S_V - \mu_V I_V
\end{align*}
\] 

3 Analysis of the Model

Based on the fact that the model monitors human and mosquito populations (living populations), all the state variables and parameters are assumed to be non-negative, $\forall \ t \geq 0$. The model is studied in the feasible region

$\Omega = (S_H, I_M, I_P, I^d, I_V, S_V) \in \mathbb{R}^7_+: N(t) \leq \frac{\Lambda_H}{\mu_H}, N_V \leq \frac{\Lambda_V}{\mu_V}$.

Which is positively-invariant set for the model (4) and hence the model is Mathematically well posed and Biologically meaningful. Solutions of the model remain positive for all the time $t \geq 0$ and are uniformly bounded in
Misdiagnosis of pneumonia as malaria

Ω. Thus we find it sufficient to consider the dynamics of the model (4) in this positive invariant domain Ω.

Let the initial data be 

\((S_H, S_v)(0) > 0, (I_M, I_{MP}, I^d, I_P, I_V)(0) \geq 0 \in \Omega)\)

Then the solution set \((S_H, S_v)(0) > 0, (I_M, I_{MP}, I^d, I_P, I_V)\) of system (4) is positive for all \(t \geq 0\)

3.1 Local stability of the disease-free equilibrium

In a situation of no disease with all the infective classes set to zero the disease free equilibrium of the model (4) denoted by \(D_0\) is given by

\(D_0 = (S_H, I_M, I_P, I^d, I_{MP}, S_V, I_V) = (\frac{\Lambda_H}{\mu_H}, 0, 0, 0, 0, \frac{\Lambda_V}{\mu_V}, 0)\)

and the local behaviour of the system at or near the DFE is determined based on the threshold parameter the basic reproduction number \(R_{MP}\) [10], and in calculating \(R_{MP}\) we use the next generation method [11] and the matrices \(F\) and \(V\) associated with the next generation method are as given below.

\[F = \begin{pmatrix}
0 & 0 & 0 & 0 & ac \\
0 & \beta & \beta \psi & \beta \sigma & 0 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
r_1 & 0 & 0 & 0 & 0 \\
r_4 & 0 & 0 & 0 & 0
\end{pmatrix}\]

and \(V = \begin{pmatrix}
0 & -\rho & r_5 \\
r_1 & 0 & 0 & 0 \\
r_4 & 0 & 0 & 0 \\
r_3 & 0 & 0 & 0 & 0 \\
mu_V & 0 & 0 & 0 & 0
\end{pmatrix}\)

Where \(r_1 = q + \delta_M + \mu_H, r_3 = \xi + \theta \delta_M + \mu_H, r_4 = \rho + \delta_P + \mu_H, r_5 = \omega \delta_P + \mu_H\).

The eigenvalues of the matrix \(FV^{-1}\) are 0, 0, \(\pm \frac{c \sqrt{a \Lambda_V \mu_H}}{\sqrt{\mu^2 \Lambda_h (\delta_M + \mu_H + q)}}\) and \(\frac{\beta}{\delta_P + \mu_H + \rho} + \frac{\beta \rho \psi}{(\delta_P + \mu_H + \rho)(\mu_H + \omega \delta_P)}\). The reproduction number \(R_{MP}\) which is the spectral radius of matrix \(FV^{-1}\) is given by \(R_{MP} = \max\{R_M, R_P\}\). Thus

\[R_{MP} = \max\left\{\frac{c \sqrt{a \Lambda_V \mu_H}}{\sqrt{\mu^2 \Lambda_h (\delta_M + \mu_H + q)}}, \frac{\beta}{\delta_P + \mu_H + \rho} + \frac{\beta \rho \psi}{(\delta_P + \mu_H + \rho)(\mu_H + \omega \delta_P)}\right\}\]

where

\[R_M = \frac{c \sqrt{a \Lambda_V \mu_H}}{\sqrt{\mu^2 \Lambda_h (\delta_M + \mu_H + q)}}\]

and

\[R_{MP} = R_P = \frac{\beta}{\delta_P + \mu_H + \rho} + \frac{\beta \rho \psi}{(\delta_P + \mu_H + \rho)(\mu_H + \omega \delta_P)}\]
The reproduction number \( R_M \) gives the number of secondary malaria infectious cases produced by a malaria infectious individual during her/his infectious period when introduced in a completely malaria susceptible population. Likewise \( R_P \) gives the number of new infections generated by a single pneumonia infected individual in a fully susceptible population [11] The disease free equilibrium \( D^0 \) of the model (4) is locally asymptotically stable (LAS) if \( R_{MP} < 1 \) and unstable if \( R_{MP} > 1 \).

3.2 Global stability of the disease-free equilibrium

Let us consider a situation where the anti-malarials are in use such that most malaria infections are treated hence the possibility of global stability at DFE for a situation where there is continued pneumonia infection transmission but a supposedly more controlled malaria is analyzed. In the study of the global behaviour of the model (4) we use the theorem by Castillo-chavez et al [3]. The model (4) is re-written as

\[
\begin{align*}
\frac{dX}{dt} &= W(X, Z), \\
\frac{dZ}{dt} &= M(X, Z), M(X, 0) = 0
\end{align*}
\]

where \( X = (S_H, S_V) \) and \( Z = (I_M, I_P, I^d, I_{MP}, I_V) \) in which the components of \( X \in \mathbb{R}^2 \) denotes the number of uninfected individuals and the components of \( Z \in \mathbb{R}^5 \) denote the number of the infected individuals, with \( D^0 = (X^*, 0) \) denoting the disease free equilibrium of this system.

\[
D^0 = (X^*, 0) \text{ where } X^* = \left(\frac{\Lambda_H}{\mu_H}, \frac{\Lambda_V}{\mu_V}\right)
\]

The conditions in (8) must be met to guarantee a local asymptotic stability:

\[
\begin{align*}
\frac{dX}{dt} &= W(X, 0), X^* \text{ is globally asymptotically stable (GAS)} \\
M(X, Z) &= AZ - \hat{M}(X, Z), \hat{M}(X, Z) \geq 0 \text{ for } (X, Z) \in \Omega
\end{align*}
\]

where \( A = D_z M(X^*, 0) \) is an M-matrix (the off-diagonal elements of \( A \) are non-negative) and \( \Omega \) is the region where the model makes biological sense. If the system (6) satisfies the conditions of (8) then the fixed point \( D^0 = (X^*, 0) \) is a globally asymptotically stable equilibrium of system (6) provided that \( R_{MP} < 1 \) and the assumptions in (8) are satisfied.

**Proof.** Consider

\[
W(X, 0) = \begin{pmatrix}
\Lambda_H - \mu_H S_H \\
\Lambda_V - \mu_V S_V
\end{pmatrix}
\]
and
\[ M(X, Z) = AZ - \hat{M}(X, Z) \]
where
\[
A = \begin{pmatrix}
  -r_1 & 0 & 0 & 0 & ac \\
  0 & r_2 & \beta \psi & 0 & 0 \\
  0 & \rho & -r_4 & \xi & 0 \\
  0 & 0 & 0 & -r_3 & 0 \\
  \var& 0 & 0 & -\var& -\mu
\end{pmatrix}
\]
and
\[
\hat{M}(X, Z) = \begin{pmatrix}
  \hat{M}_1(X, Z) \\
  \hat{M}_2(X, Z) \\
  \hat{M}_3(X, Z) \\
  \hat{M}_4(X, Z) \\
  \hat{M}_5(X, Z)
\end{pmatrix} = \begin{pmatrix}
  acI_V(1 - \frac{S_H}{N_H}) \\
  \beta(I_P + \psi(I^d) + \sigma I_{MP}(1 - \frac{S_H}{N_H})) \\
  \gamma\lambda M^d \\
  -\gamma\lambda M^d \\
  \var\lambda(\lambda^I + \pi I_{MP})(1 - \frac{S_V}{N_H})
\end{pmatrix}
\]
Thus \( \hat{M}_1, \hat{M}_2, \hat{M}_3, \hat{M}_5 > 0 \), but \( \hat{M}_4 < 0 \). The conditions in (8) are not satisfied, since \( \hat{M}(X, Z) < 0 \) and hence \( D^0 \) may not be globally asymptotically stable.

In the case of the double malaria-pneumonia infection or malaria-pneumonia concurrent infection the DFE may not be globally asymptotically stable in \( \Omega \) for \( R_{MP} < 1 \) due to possible occurrence of backward bifurcation at \( R_{MP} = 1 \) [15]. And particularly in a case like this where there is sufficiently large disease induced death rate [3] because of untreated pneumonia.

4 Endemic Equilibrium and Stability analysis

We employ the Center Manifold theorem [3, 7]

Consider the following general system of ordinary differential equations with a parameter \( \eta \)
\[
\frac{dx}{dt} = f(x, \eta), \ f : \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R}^n \text{ and } f \in C^2(\mathbb{R}^n \times \mathbb{R}) \tag{9}
\]

Where 0 is an equilibrium point for system (4) for all values of the parameter \( \eta \), that is \( f(0, \eta) \equiv 0 \) and

1. \( G = D_x f(0, 0) = \frac{\partial f}{\partial x} (0, 0) \) is the linearization matrix of the system around the equilibrium point 0 with \( \eta \) evaluated at 0;
2. Zero is a simple eigenvalue of $G$ and all other eigenvalues of $G$ have negative real parts;

3. Matrix $G$ has a right eigenvector $w$ and a left eigenvector $v$ corresponding to the zero eigenvalue.

Let $f_k$ be the $k$th component of $f$ and

\[
\varrho^* = \sum_{kij=1}^n v_kw_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0)
\]

\[
l^* = \sum_{ki=1}^n v_kw_i \frac{\partial^2 f_k}{\partial x_i \partial \rho_B}(0,0)
\]

then, the local dynamics of the system around the equilibrium point 0 is entirely determined by the signs of $\varrho^*$ and $l^*$, and especially if $\varrho^* > 0$ and $l^* > 0$ then a backward bifurcation occurs. Particularly when:

1. $l^* > 0$, $\varrho^* > 0$, when $\rho_B < 0$ with $|\rho_B| \ll 1$, $(0,0)$ is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \rho_B \ll 1$, $(0,0)$ is unstable and there exists a negative and locally asymptotically stable equilibrium.

2. $l^* < 0$, $\varrho^* < 0$, when $\rho_B < 0$ with $|\rho_B| \ll 1$, $(0,0)$ is unstable; when $0 < \rho_B \ll 1$, $(0,0)$ is asymptotically stable and there exists a positive unstable equilibrium.

3. $l^* > 0$, $\varrho^* < 0$, when $\rho_B < 0$ with $|\rho_B| \ll 1$, $(0,0)$ is unstable, and there exists a negative and locally asymptotically stable equilibrium; when $0 < \rho_B \ll 1$, $(0,0)$ is stable and there exists a positive unstable equilibrium.

4. $l^* < 0$, $\varrho^* > 0$, when $\rho_B$ changes from negative to positive, $(0,0)$ changes its stability from stable to unstable. Correspondingly a negative equilibrium becomes positive and locally asymptotically stable.

To apply the Center Manifold approach we make the following variable changes. Let $S_H = x_1$, $I_M = x_2$, $I_P = x_3$, $I^d = x_4$, $I_{MP} = x_5$, $S_V = x_6$, $I_V = x_7$ and thus $N_H = x_1 + x_2 + x_3 + x_4 + x_5$ and $N_V = x_6 + x_7$. We can therefore re-write the model system 3.1.4 in the form $\frac{dx}{dt} = F(x)$ where $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7)$ and $F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7)$ as follows
where
\[
\begin{align*}
\frac{dx_1}{dt} &= f_1 = \Lambda_H + q x_2 - \frac{ac x_7 x_1}{x_1 + \ldots + x_5} - \frac{\beta x_1 (x_3 + \psi x_4 + \sigma x_5)}{x_1 + \ldots + x_5} - \mu_H x_1 \\
\frac{dx_2}{dt} &= f_2 = \frac{ac x_2 x_1}{x_1 + \ldots + x_5} - (q + \delta_M + \mu_H) x_2 \\
\frac{dx_3}{dt} &= f_3 = \frac{\beta (x_3 + \psi x_4 + \sigma x_5) x_1}{x_1 + \ldots + x_5} - (\rho + \delta_P + \mu_H) x_3 \\
\frac{dx_4}{dt} &= f_4 = \frac{\gamma ac x_7 x_4}{x_1 + \ldots + x_5} - (\omega \delta_P + \mu_H) x_4 + \xi x_5 \\
\frac{dx_5}{dt} &= f_5 = \frac{\gamma ac x_7 x_4}{x_1 + \ldots + x_5} - (\xi + \theta \delta_{MP} + \mu_H) x_5 \\
\frac{dx_6}{dt} &= f_6 = \Lambda_V - \mu_V x_6 - \frac{\vartheta c (x_1 + y x_5) x_6}{x_1 + \ldots + x_5} \\
\frac{dx_7}{dt} &= f_7 = \frac{\vartheta c (x_2 + y x_5) x_6}{x_1 + \ldots + x_5} - \mu_V x_7
\end{align*}
\]

The Jacobian of the system (10) at disease free equilibrium is as below
\[
\begin{pmatrix}
-\mu_H & q & \beta & -\beta \psi & -\beta \sigma & 0 & -ac \\
0 & -r_1 & 0 & 0 & 0 & 0 & ac \\
0 & 0 & r_2 & \beta \varphi & \beta \sigma & 0 & 0 \\
0 & 0 & \rho & -r_4 & \xi & 0 & 0 \\
0 & 0 & 0 & 0 & -r_3 & 0 & 0 \\
0 & -\vartheta c T & 0 & 0 & -\vartheta c y T & -\mu_V & 0 \\
0 & -\vartheta c T & 0 & 0 & -\vartheta c y T & 0 & -\mu_V
\end{pmatrix}
\]

From which it can be shown that the basic reproduction number is
\[
R_{MP} = R_P = \frac{\beta (\mu_H + \omega \delta_P + \rho \psi)}{(\delta_P + \mu_H + \rho)(\mu_H + \omega \delta_P)} \quad (11)
\]

Taking \(\rho = \rho_B\) as a bifurcation parameter, then we can solve for \(\rho\) from \(R_{MP} = 1\) which is also the bifurcation point and get
\[
\rho = \rho_B = \frac{\mu_H (\beta - \delta_P - \mu_H - \omega \delta_P) + \omega \delta_P (\beta - \delta_P)}{\mu_H + \omega \delta_P - \beta \psi} \quad (12)
\]
We can show that the Jacobian of the system has a right eigenvector given by \( w = (w_1, w_2, w_3, w_4, w_5, w_6, w_7)^T \) where

\[
\begin{align*}
    w_1 &= \frac{w_2(ac^2\partial T) - q}{\mu V} - \frac{(\psi\mu_H^2 + \beta\psi)\beta w_3}{\psi\mu_H^3} \\
    w_2 &= w_2 > 0 \\
    w_3 &= \frac{-\beta\psi w_4}{r_2} \\
    w_4 &= \frac{\beta w_3}{r_4} \\
    w_5 &= 0 \\
    w_6 &= \frac{-\partial cT w_2}{\mu V} \\
    w_7 &= \frac{\partial cT w_2}{\mu V}
\end{align*}
\]

and a left eigenvector \( v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7)^T \), where

\[
\begin{align*}
    v_1 &= 0 \\
    v_2 &= v_2 > 0 \\
    v_3 &= -\frac{\rho v_4}{r_2} \\
    v_4 &= -\frac{r_2 v_3}{\rho} \\
    v_5 &= \frac{(\xi r_2 - \beta\psi \rho)v_4}{r_2 r_3} + \frac{ac^2\partial T v_2}{\mu V} \\
    v_6 &= 0 \\
    v_7 &= \frac{acv_2}{\mu V}
\end{align*}
\]

After some manipulation involving the evaluation of the associated non-vanishing partial derivatives of \( f \) it can be shown that

\[
\varrho^* = \frac{\mu_H}{\Lambda_H} (v_5 + v_7 w_2 w_6 a c - v_4) > 0 \quad (13)
\]

and

\[
l^* = w_3 (v_3 + \psi v_4) > 0 \quad (14)
\]

thus \( \varrho^* > 0 \) and \( l^* > 0 \) and the following result is ascertained. If \( \varrho^* \) and \( l^* \) satisfy the inequalities given in (13) and (14) then, the model (4) undergoes a backward bifurcation that occurs at \( R_{MP} = 1 \).
4.1 Sensitivity Analysis of \( (R_{MP}) \)

We perform sensitivity analysis in order to determine the parameters which have high impact on \( R_{MP} \) that should be targeted for intervention strategies. In order to determine how best to reduce human mortality and morbidity due to pneumonia, it is necessary to know the relative importance of the different factors responsible for its spread and prevalence. The sensitivity indices of the reproduction number are computed using the approach by Chitnis [9] as follows:

\[
\tau^R_{BP} = \frac{\partial R_{MP}}{\partial B} \frac{B}{R_{MP}},
\]

(15)

to each of the parameters \( \delta_P, \psi, \rho, \varpi \). For example the sensitivity index of \( R_{MP} \) to the parameter \( \rho \) is given by

\[
\tau^R_{MP} = \frac{\partial R_{MP}}{\partial \rho} \frac{\rho}{R_{MP}} = \frac{\rho r_4 r_5 \ln r_4 + \psi}{r_5 + \rho \psi}.
\]

(16)

Similarly we compute sensitivity indices of the reproduction number \( R_{MP} \) to the parameters \( \delta_P, \psi \) and \( \varpi \) and compare the results to find out the most sensitive parameter. The sensitivity indices to the parameters and the values of the respective parameters used are given in Table 1

<table>
<thead>
<tr>
<th>parameters</th>
<th>value</th>
<th>reference</th>
<th>sensitivity index</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \delta_P )</td>
<td>( 7.8335 \times 10^{-4} ) day(^{-1} )</td>
<td>Assumed</td>
<td>(-4.938 \times 10^{-4})</td>
</tr>
<tr>
<td>( \psi )</td>
<td>0.00021 day(^{-1})</td>
<td>Assumed</td>
<td>2.0785 \times 10^{-4}</td>
</tr>
<tr>
<td>( \rho )</td>
<td>0.08 day(^{-1})</td>
<td>[8]</td>
<td>1.9255 \times 10^{-1}</td>
</tr>
<tr>
<td>( \varpi )</td>
<td>1.00005 day(^{-1})</td>
<td>Assumed</td>
<td>(-1.6006 \times 10^{-5})</td>
</tr>
</tbody>
</table>

Table 1: Sensitivity indices.

The most sensitive parameter is the misdiagnosis rate \( \rho \). This suggests that accurate diagnosis in treatment of pneumonia has positive impact in controlling pneumonia in the community. Reducing the rate of misdiagnosis through laboratory tests would have the largest effect on pneumonia transmission. It can also be noted that the moment \( \rho \) increases or decreases, \( \psi \) also increases or decreases considerably.
5 A case of prompt and accurate diagnosis of pneumonia, $\rho \approx 0$

5.1 Local Stability of Disease-Free Equilibrium

After analyzing the model system of misdiagnosis it is in order to gain insight into the dynamics of the pneumonia-malaria concurrent and co-infection model in which pneumonia is promptly and accurately diagnosed and treatment given in time. We have the model where $I^d = I_{MP} = 0$ given by

$$
\frac{dS_H}{dt} = \Lambda_H - \lambda_M S_H - \lambda_P S_H - \mu_H S_H + q I_M \\
\frac{dI_M}{dt} = \lambda_M S_H - \delta_M I_M - \mu_H I_M - q I_M \\
\frac{dI_P}{dt} = \lambda_P S_H - h_P I_P - \delta_P I_P - \mu_H I_P \\
\frac{dS_V}{dt} = \Lambda_V - \mu_V S_V - \lambda_V S_V \\
\frac{dI_V}{dt} = \lambda_V S_V - \mu_V I_V
$$

(17)

Where

$$
\lambda_M = \frac{acI_V}{N_H} \\
\lambda_P = \frac{\beta I_P}{N_H} \\
\lambda_V = \frac{\vartheta a I_M}{N_H}
$$

and the total population of humans and the vector are given by $N_H = S_H + I_M + I_P$ and $N_V = S_V + I_V$ respectively. $h_P$ is the rate at which those pneumonia infectious persons get healed on receiving treatment and join the susceptible.

The region $\phi_T = (S_H, I_M, I_V, I_P, S_V) \in \mathbb{R}^5_+: N_H \leq \frac{\Lambda_H}{\mu_H}, N_V \leq \frac{\Lambda_V}{\mu_V}$ is positively invariant and attracting and the solution starting in $\phi_T$ approach, enter or stay in $\phi_T$. Thus the dynamics of the model 17 is analyzed in $\phi_T$. The DFE is given as

$$
D_0 = (S_H, I_M, I_P, I_V, S_V) = \left( \frac{\Lambda_H}{\mu_H}, 0, 0, 0, \frac{\Lambda_V}{\mu_V} \right)
$$

We use the next generation approach to determine the reproduction number $R^{+}_{MP}$. Thus we have;
\[ F = \begin{pmatrix} 0 & 0 & ac \\ 0 & \beta & 0 \\ \vartheta cT & 0 & 0 \end{pmatrix} \]

and
\[ V = \begin{pmatrix} r_1 & 0 & 0 \\ 0 & r_6 & 0 \\ 0 & 0 & \mu_H \end{pmatrix} \]

The eigenvalues of the matrix \( FV^{-1} \) are
\[ \frac{\beta}{n_T+\delta p+\mu_H} \text{ and } \pm \sqrt{\frac{ac^2 \lambda_v \mu_H}{\mu \lambda_v (\delta_T+\mu_H+q)}} \]

Therefore the reproduction number \( R_{MP}^{+} \) which is the spectral radius of matrix \( FV^{-1} \) is given by
\[ R_{MP}^{+} = \max \{ R_M, R_P \} \]

Where
\[ R_M = \sqrt{\frac{ac^2 \lambda_v \mu_H}{\mu \lambda_v (\delta_T+\mu_H+q)}} \text{ and } R_P = \frac{\beta}{n_T+\delta p+\mu_H} \]

Consequently the reproduction number associated with pneumonia is
\[ R_{MP}^{+} = \beta + \delta p + \mu_H. \]

The disease-free equilibrium \( D^0 \) is locally asymptotically stable (LAS) when \( R_{MP}^{+} < 1 \) and unstable when \( R_{MP}^{+} > 1 \).

We observe that
\[ R_{MP}^{+} = \frac{\beta}{n_T+\delta p+\mu_H} \ll R_{MP}^{-} = \frac{\beta}{\delta_T+\mu_H+\rho} + \frac{\beta \rho \psi}{(\delta_T+\mu_H+\rho)(\mu_H+\omega \delta)} \]

It can be noted that as \( \rho \) increases, the rate at which susceptible individuals are infected with pneumonia also increases.

### 5.2 Global Stability of DFE

The DFE \([D^0]\) of model (17) is globally asymptotically stable (GAS) whenever \( R_{MP}^{+} < 1 \) and unstable if \( R_{MP}^{+} > 1 \). We use comparison theorem [12] to prove the above statement.

The equation of the infected components in the model (17) can be written as
\[ \begin{pmatrix} \frac{dI_M}{dt} \\ \frac{dI_P}{dt} \\ \frac{dI_V}{dt} \end{pmatrix} = (F - V) \begin{pmatrix} I_M \\ I_P \\ I_V \end{pmatrix} - (1 - \frac{S}{N}) \begin{pmatrix} ac & 0 & 0 \\ 0 & \beta & 0 \\ \vartheta cT & 0 & 0 \end{pmatrix} \]

Where \( F \) and \( V \) are as defined in subsection (5.1) and
\[ F - V = \begin{pmatrix} -r_1 & 0 & ac \\ 0 & \beta - r_6 & 0 \\ \vartheta cT & 0 & -\mu_H \end{pmatrix} \]

Since \( S \leq N \forall t \geq 0 \) in \( \phi_T \) then
\[ \begin{pmatrix} \frac{dI_M}{dt} \\ \frac{dI_P}{dt} \\ \frac{dI_V}{dt} \end{pmatrix} \leq (F - V) \begin{pmatrix} I_M \\ I_P \\ I_V \end{pmatrix} \]
From the fact that eigenvalues of the matrix $F - V$ all have negative real parts, it follows that the linearized differential inequality system is stable whenever $R_P < 1$. Consequently $(I_M, I_P, I_V) \to (0,0,0)$ as $t \to \infty$. This is contrary to the case of misdiagnosis of pneumonia where the DFE is globally asymptotically unstable and a backward bifurcation occurs.

5.3 Global stability of endemic equilibrium

In this section we study the global stability of the endemic equilibrium of model (17) using the Lyapunov second method also known as Lyapunov direct method. We use the Lyapunov function $L_e(x_1, x_2, x_3, \ldots x_n) = \sum_{i=1}^{n} C_i(x_i - x_i^* - x_i^* \log \frac{x_i}{x_i^*})$ to prove the global stability of the endemic equilibrium $E^*(S_H^*, I_M^*, I_P^*, S_V^*, I_V^*)$. If $R_0 > 1$ then the unique endemic steady state $E^*$ of (17) is Globally Asymptotically stable in the interior of $\phi_T$: Define Lyapunov function

$$L_e : (S_H, I_M, I_P, S_V, I_V) \in \phi_T : S_H, I_M, I_P, S_V, I_V > 0 \to \mathbb{R}$$

by

$$L_e(S_H, I_M, I_P, S_V, I_V) = \lambda_V(S_H - S^*_H + S^*_H \log \frac{S_H}{S^*_H}) + \lambda_V(I_M - I^*_M + I^*_M \log \frac{I_M}{I^*_M})$$

$$+ \lambda_V(I_P - I^*_P + I^*_P \log \frac{I_P}{I^*_P}) + \lambda_M(S_V - S^*_V + S^*_V \log \frac{S_V}{S^*_V})$$

$$+ \lambda_M(I_V - I^*_V + I^*_V \log \frac{I_V}{I^*_V})$$

$L_e$ is $C^1$ on the interior of $\phi_T$, $E^*$ is the global minimum of $L_e$ on $\phi_T$ and $L_e : (S_H^*, I_M^*, I_P^*, S_V^*, I_V^*) = 0$. The time derivative of $L_e$ computed along the solution of model (17) is

$$\frac{dL_e}{dt} = \lambda_V(1 - \frac{S^*_H}{S_H}) \frac{dS_H}{dt} + \lambda_V(1 - \frac{I^*_M}{I_M}) \frac{dI_M}{dt} + \lambda_V(1 - \frac{I^*_P}{I_P}) \frac{dI_P}{dt} + \lambda_M(1 - \frac{S^*_V}{S_V}) \frac{dS_V}{dt} + \lambda_M(1 - \frac{I^*_V}{I_V}) \frac{dI_V}{dt}$$

$$\frac{dL_e}{dt} = \lambda_V(1 - \frac{S^*_H}{S_H})(\Lambda_H - (\lambda_M + \lambda_P + \mu_H)S_H + qI_M) + \lambda_V(1 - \frac{I^*_P}{I_P})(\lambda_P S_H - (h_P + \delta_P + \mu_H)I_P) + \lambda_M(1 - \frac{S^*_V}{S_V})(\Lambda_V - (\mu_V + \lambda_V)S_V) + \lambda_M(1 - \frac{I^*_V}{I_V})(\Lambda_V S_V - \mu_V I_V)$$

Using $\Lambda_H = (\lambda_M + \lambda_P + \mu_H)S_H^* + qI^*$, $\Lambda_V = (\mu_V + \nu S_V^*)$ to rewrite this, we get

$$\frac{dL_e}{dt} = -\lambda_V(\frac{S^*_H}{S_H})^2(\lambda_M + \lambda_P + \mu_H) + \lambda_V(1 - \frac{I^*_M}{I_M})(\lambda_M S_H - \nu_I I_M) + \lambda_V(1 - \frac{I^*_P}{I_P})(\lambda_P S_H - (h_P + \delta_P + \mu_H)I_P) - \lambda_M(\frac{S^*_V}{S_V})^2(\lambda_V - \nu_V) + \lambda_M(1 - \frac{I^*_V}{I_V})(\lambda_V S_V - \mu_V I_V) \leq 0$$
\[ \lambda_v \frac{(I_P - I_P^*)}{I_P} (\lambda_v S_H - (h_P + \delta_P + \mu_H)I_P) \] is negative since due to correct diagnosis \( h_P \rightarrow \infty \) as \( \lambda_P \rightarrow 0 \). Which is the same case with \( \lambda_v \frac{(I_M - I_M^*)}{I_M} (\lambda_M S_H - r_1 I_M) \), as \( q \rightarrow \infty \) due to the availability of anti-malaria \( \lambda_M \rightarrow 0 \). Which is the same case with \( \lambda_v \frac{(I_M - I_M^*)}{I_M} (\lambda_M S_H - r_1 I_M) \), as \( q \rightarrow \infty \) due to the availability of anti-malaria \( \lambda_M \rightarrow 0 \).

\[ \frac{dL}{dt} \] is less or equal to zero with equality only if \( S_H = S_H^*, I_M = I_M^*, I_P = I_P^*, S_V = S_V^* \) and \( I_V = I_V^* \).

Hence the largest compact invariant set in \( (S_H, I_M, I_P, S_V, I_V) \in \phi_T : \frac{dL}{dt} = 0 \) is only \( E^* \), where \( E^* \) is the endemic equilibrium point. This implies that by the asymptotic stability theorem [1], the endemic steady state \( E^* \) is globally asymptotically stable in the interior of \( \phi_T \).

### 6 Numerical simulations

In this section we use numerical simulation in order to give graphical projection of the results of the model (4). Some of the parameters were obtained from literature, some were assumed or made varying for realistic simulation results. The parameter values used are in Table 2.

<table>
<thead>
<tr>
<th>Parameter Description</th>
<th>Symbol</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human recruitment rate</td>
<td>( \Lambda_H )</td>
<td>( 8.748 \times 10^{-3} \text{day}^{-1} )</td>
<td>[4]</td>
</tr>
<tr>
<td>Mosquito recruitment rate</td>
<td>( \Lambda_V )</td>
<td>( 0.071 \text{day}^{-1} )</td>
<td>[6]</td>
</tr>
<tr>
<td>Human natural mortality rate</td>
<td>( \mu_H )</td>
<td>( 2.740 \times 10^{-3} \text{day}^{-1} )</td>
<td>[4]</td>
</tr>
<tr>
<td>Mosquito natural mortality rate</td>
<td>( \mu_V )</td>
<td>( 0.1429 \text{day}^{-1} )</td>
<td>[9]</td>
</tr>
<tr>
<td>Transmission probability</td>
<td>( a )</td>
<td>( 0.5 \text{day}^{-1} )</td>
<td>[9]</td>
</tr>
<tr>
<td>for malaria in humans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biting rate of mosquito</td>
<td>( c )</td>
<td>( 0.125 \text{day}^{-1} )</td>
<td>Assumed</td>
</tr>
<tr>
<td>Transmission probability</td>
<td>( \vartheta )</td>
<td>\text{Variable} \text{day}^{-1}</td>
<td>Variable</td>
</tr>
<tr>
<td>for malaria in mosquitoes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia contact rate</td>
<td>( \beta )</td>
<td>\text{Variable} \text{day}^{-1}</td>
<td>Variable</td>
</tr>
<tr>
<td>Rate of misdiagnosis</td>
<td>( \rho )</td>
<td>( 0.08 \text{day}^{-1} )</td>
<td>Estimate</td>
</tr>
<tr>
<td>Malaria induced death rate</td>
<td>( \delta_M )</td>
<td>( 4.49312 \times 10^{-4} \text{day}^{-1} )</td>
<td>[6]</td>
</tr>
<tr>
<td>Pneumonia induced death rate</td>
<td>( \delta_P )</td>
<td>( 7.8335 \times 10^{-4} \text{day}^{-1} )</td>
<td>[14]</td>
</tr>
<tr>
<td>Pneumonia and malaria induced death rate</td>
<td>( \delta_{MP} )</td>
<td>( 9.6445 \times 10^{-4} \text{day}^{-1} )</td>
<td></td>
</tr>
<tr>
<td>Recovery rate from malaria</td>
<td>( q )</td>
<td>( 0.00655 \text{day}^{-1} )</td>
<td>Assumed</td>
</tr>
<tr>
<td>Modification parameters</td>
<td>( \psi, \sigma, \pi )</td>
<td>( 0.00021, 0.00025, 0.007 )</td>
<td>Assumed</td>
</tr>
<tr>
<td>Modification parameters</td>
<td>( \varpi, \theta, \gamma )</td>
<td>( 1.00005, 0.05, 0.8883 )</td>
<td>Assumed</td>
</tr>
</tbody>
</table>

Table 2: Parameter values.
6.1 The effect of increasing misdiagnosis on malaria transmission

Figure 1: Simulations of model (4) with increasing levels of misdiagnosis, with $\rho = 0.000$, $\rho = 0.080$, $\rho = 1.080$, $\rho = 2.080$
It is evident that increasing rates of misdiagnosis of pneumonia result into increased pneumonia infection.

Figure 2: Simulation of effect of misdiagnosing of pneumonia as malaria. Despite the overuse of anti-malaria, malaria persists and rises with rise in rate of misdiagnosis
6.2 The effect of increasing misdiagnosis on the spread of pneumonia

![Figure 3: Simulations of malaria and pneumonia with increasing misdiagnosis, with $\rho = 0.0800$, $\rho = 1.080$, $\rho = 2.080$, $\rho = 4.080$]

In the presence of pneumonia, malaria persists despite malaria treatment.

![Figure 4: Simulation of model (4) showing the plots of the dynamical evolution of pneumonia in the different classes against time]

Figure 4: Simulation of model (4) showing the plots of the dynamical evolution of pneumonia in the different classes against time
Figure 5: Simulation of model (4) comparing Pneumonia and malaria in the presence of increasing misdiagnosis of pneumonia

6.3 The effect of varying the pneumonia contact rate, $\beta$

Figure 6: A higher contact rate greatly increases pneumonia infectives, and the more the misdiagnosis, the higher the contact rate, $\beta_p$
7 Discussion

In many health facilities especially peripheral health centers, a diagnosis of malaria is based solely on clinical features such as fevers [2]. Although the approach may reduce morbidity, many infectious diseases mimic malaria and this strategy leads to high rates of over-diagnosis and over-treatment of malaria with consequent under-diagnosis of other fever causing disorders such as pneumonia and typhoid. The work has addressed the co-dynamics between malaria and pneumonia using deterministic mathematical model which incorporates the intricate issue of misdiagnosing pneumonia as malaria.

An important epidemic threshold parameter $R_0$, the basic reproduction number which indicates the population level impact of an infectious disease classifies the long term progression of the disease. When $R_0 < 1$ and when $R_0 > 1$ the DFE is stable and unstable respectively.

From the results of subsection 3.2, there is evidence that the basic reproduction number being less than unity $R_{MP} < 1$ alone does not guarantee the global dynamics of the disease transmission. The global stability of the DFE steady state does not hold due to the model undergoing backward bifurcation. A backward bifurcation occurs when the delayed effect for treatment is strong. Therefore driving $R_{MP}$ value below one is not enough to eradicate the disease. When pneumonia is not diagnosed the infected continue to mingle with the susceptible and continue infecting them. Worse still the concentration of the bacteria in the pneumonia infected persons rises and this makes the misdiagnosed persons even more infectious, infecting a greater number of people as seen in figure 1. Those admitted with misdiagnosed pneumonia are even a greater risk because they are put together with other sick people who have weak immune response and are highly pre-disposed to pneumonia infection. Incidences of hospital pneumonia are much greater and fatal. The backward bifurcation in a disease model has important qualitative implications. Small changes in certain parameters can produce large changes in equilibrium behaviour. In backward bifurcation when the $R_{MP}$ just gets greater than one the disease can invade to relatively high endemic level.

In $R_{MP}$ the most sensitive parameter after an individual has got into contact with pneumonia is the rate of misdiagnosis $\rho$, increasing or decreasing $\rho$ also increases or decreases $R_{MP}$. Despite extensive use of anti-malarials, the presence of pneumonia enhances the existence of malaria. The compromised immunity of the pneumonia infectives makes them easy to infect as seen in figure 2 and figure 3. Also pneumonia induced increase in susceptibility to malaria infection significantly increases the number of new cases of the dual malaria pneumonia co-infection as in figure 5. A double infection with malaria worsens the condition and makes the individual even more infectious. Comparing the reproduction number $R_{MP} = \frac{\beta}{\delta_p + \mu_H + \rho} + \frac{\beta \rho \psi}{(\delta_p + \mu_H + \rho)(\mu_H + \omega \delta_p)}$ with the
one where there is accurate diagnosis, $R_{MP}^+$, the time an individual takes with pneumonia $\frac{1}{\delta_P + \mu_H + \rho} + \frac{\rho \psi}{(\delta_P + \mu_H + \rho)(\mu_H + \omega \delta_P)}$ has increased thus raising the probability of infecting more people, consequently increasing $\beta$ the effective contact rate with pneumonia infectious person, which continues to increase $R_{MP}$ and causes pneumonia to reach high endemic levels.

A slight increase in $\beta$ which is occasioned by the increase of $\rho$ increases $R_{MP}$ to a value greater than unity, and consequently pneumonia rises to high endemic levels. And since there is a high percentage of misdiagnosing pneumonia as malaria, the level of pneumonia infection rises, and also the longer one stays with pneumonia the more infectious one becomes. And because of no treatment $\delta_P$ and $\delta_{MP}$ increases compounded by the fact that pneumonia is a fast killer.

8 Conclusion

A major conclusion from our study is that if there is accurate diagnosis of pneumonia then both pneumonia and malaria can be reduced if the basic reproduction number is reduced below unity. If there is any degree of misdiagnosis of pneumonia then $R_{MP} < 1$ alone is not sufficient for the diseases to be eliminated since there are high chances of backward bifurcation occurring.

The recent commissioned pneumonia vaccine may not benefit the majority of Kenyans due to its exorbitant cost and no equipment for its delivery and storage in the more easily accessible health centers. This translates into increased susceptibility to pneumonia. And since pneumonia is highly infectious, which is elevated by the nature of our habitat (highly dusty and never disinfected) and fatal, many more lives continue to be lost particularly due to it being misdiagnosed as malaria. 1.36 million children alone lose their lives from pneumonia yearly. Yet the pneumonia treating drugs are quite affordable.

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References


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