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A Model on the Impact of Treating Typhoid with Anti-malarial: Dynamics of Malaria Concurrent and Co-infection with Typhoid

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Abstract

In this paper we have formulated a mathematical model of malaria-typhoid concurrent and co-infection to establish the effect of misdiagnosing typhoid as malaria and hence treating it with anti-malarials.

We establish the existence of equilibria points in terms of the basic reproduction number R_{MT}. The DFE is locally asymptotically stable if $R_{MT} < 1$ and unstable if $R_{MT} > 1$. The results show that the DFE is not globally asymptotically stable (GAS) even when $R_{MT} < 1$. Instead, backward bifurcation is shown to exist at $R_{MT} = 1$. A small perturbation at this point, $R_{MT} = 1$, due to misdiagnosis causes disease explosion. Backward bifurcation implies that having $R_{MT} < 1$, although necessary, is not sufficient for curtailing endemicity of the disease. Sensitivity analysis of the reproduction number shows that an increase in the rate of misdiagnosis results in an increase of new disease incidences. The carrier parameter is also very sensitive. A major finding of this study is that misdiagnosis of typhoid leads to high endemicity of typhoid. Moreover, despite overuse of anti-malarials, misdiagnosis enhances malaria infection. Results of this study will help health care providers understand how misdiagnosis errors are made, reduce misdiagnosis and improve patient care.

Keywords: Similar symptoms, Misdiagnosis, Carriers,Stability, Backward bifurcation

1 Introduction

In endemic areas most cases of malaria are diagnosed on clinical grounds without laboratory confirmation of parasitaemia. The diagnosis is based on the presence of fever, or history of fever. Since fever is a symptom of many illnesses, many people treated for malaria are not actually infected with malaria parasites. 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 typhoid and malaria often have symptom overlap which would otherwise necessitate dual treatment with both anti-malarials and antibiotics if proper tests were done. There are always delays in establishing the correct diagnosis as a result of the clinical status, accounting to high morbidity and mortality due to typhoid. Further more, a large proportion of typhoid fever infection takes the form of carriers. These are those people who are infected but do not show any signs of infection, but are equally infectious as the symptomatic infectives. Because of delays in treating typhoid, it is a major killer in this combination. In this study we have developed a mathematical model for the dynamics of misdiagnosis of typhoid as malaria in malaria-tyhpoid 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 total human population N_H is sub-divided into compartments, namely susceptible S_H, those infectious with malaria I_M, individuals with symptoms of typhoid I_T, those dually infected with symptomatic malaria and Typhoid I_{MT}, those infected with typhoid but are misdiagnosed for malaria I^d, and carriers of the typhoid bacteria who do not show the typhoid symptoms I^C [9]. For the vector, S_V represent the susceptible and I_V are the infectious class. The susceptible humans and mosquitoes are recruited into their populations at the rates of Λ_H and Λ_V respectively. $N_H = S_H + I_M + I_{MT} + I_T + I^C + I^d$ is the total human population, while $N_V = S_V + I_V$ represents the total vector population, at time t. Susceptible humans acquire malaria infection at the rate of λ_M and typhoid at the rate of λ_T, while mosquitoes become infectious with malaria at the rate λ_V. q is the rate of human recovery into the susceptible from being infectious with malaria. Our model excludes partial immunity. All individual humans and mosquitoes in different human and vector subgroups suffer natural death rates of μ_H and μ_V respectively. Individuals in classes I_T and I_{MT} can have their typhoid status misdiagnosed as malaria and progress to I^d class at per capita rate of ρ and ξ correspondingly. Typhoid infected individuals who have been misdiagnosed develop a much weaker immunity due to the rise in bacteria concentration thus can easily get malaria infection at the rate of $\gamma\lambda_M$, where γ is the modification parameter accounting for increased rate of malaria infection. ζ accounts for the people who become carriers on infection [9] and g accounts for the the individuals who get typhoid infection, are misdiagnosed and as the body fights the bacteria, the bacteria hides in the gallbladder [9]. These people also become carriers and keep shedding the bacteria for years, unless they get accurately diagnosed and treated. Otherwise these people can cause high endemic disease levels or even epidemic situations [4]. L is the rate at which those who happen to be treated rejoin the susceptible individuals. Individuals in the I_M and I_T classes suffer disease induced deaths at the rates δ_M and δ_T respectively. However those in I^d class suffer disease induced death at rate $\varpi\delta_T$, where ϖ accounts for increased mortality due to prolonged time taken without the right diagnosis and treatment. Individuals in I_{MT} class suffer disease induced death at the rate $\theta\delta_{MT}$ where θ accounts for accelerated deaths due to immunosuppression by the untreated typhoid and the newly acquired malaria in dual infection. Susceptible humans acquire malaria at a rate

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

where a is the transmission probability per bite and b is the per capita biting rate of mosquito. Likewise the force of infection of susceptibles with typhoid

is

$$\lambda_T = \frac{\beta(I_T + \eta I^d + \sigma I_{MT} + \alpha I^C)}{N_H} \tag{2}$$

Where β is the effective transmission rate of typhoid on contact and η, σ and α account for increased infection by a misdiagnosed, dually infected individual, and a carrier respectively. The force of infection of susceptible mosquito by infected human is given as

$$\lambda_V = \frac{\kappa b(I_M + \pi I_{MT})}{N_H}. \tag{3}$$

κ is the transmission probability for mosquito infection and b is the biting rate of mosquito, π is the modification parameter accounting for increased likelihood of infection of vectors by people in I_{MT} class. We assume no simultaneous infection. With the above definitions and assumptions, we have the following model

$$\begin{aligned}
\frac{dS_H}{dt} &= \Lambda_H + qI_M + LI_T - \lambda_M S_H - \lambda_T S_H - \zeta\lambda_T S_H - \mu_H S_H \\
\frac{dI_M}{dt} &= \lambda_M S_H - qI_M - \delta_M I_M - \mu_H I_M \\
\frac{dI_T}{dt} &= \lambda_T S_H - \rho I_T - LI_T - \delta_T I_T - \mu_H I_T \\
\frac{dI^d}{dt} &= \rho I_T + \xi I_{MT} - \gamma\lambda_M I^d - \varpi\delta_T I^d - gI^d - \mu_H I^d \\
\frac{dI_{MT}}{dt} &= \gamma\lambda_M I^d - \xi I_{MT} - \theta\delta_{MT} I_{MT} - \mu_H I_{MT} \\
\frac{dI^C}{dt} &= \zeta\lambda_T S_H + gI^C - \mu_H I^C \\
\frac{dS_V}{dt} &= \Lambda_V - \mu_V S_V - \lambda_V S_V \\
\frac{dI_V}{dt} &= \lambda_V S_V - \mu_V I_V
\end{aligned} \tag{4}$$

3 Analysis of the Model

Model (4) describes the human population and therefore it can be shown that the associated state variables are non-negative for all time $t \geq 0$ and that the solutions of the model (4) with positive initial data remains positive for all time $t \geq 0$ and are uniformly-bounded. We assume the associated parameters as non-negative for all time $t \geq 0$. Thus (4) is mathematically well posed and its dynamics can be considered in a proper subset

$\Omega = (S_H, I_M, I_T, I_{MT}, I^d, I^C, I_V, S_V) \in \mathbb{R}^8_+ : N(t) \leq \frac{\Lambda_H}{\mu_H}, N_V \leq \frac{\Lambda_V}{\mu_V}$.

Lema1: Let the initial data be
$(S_H, S_v)(0) > 0, (I_M, I_{MT}, I^d, I^C, I_T, I_V)(0) \geq 0 \in \Omega$.
Then the solution set $(S_H, S_v)(0) > 0, (I_M, I_{MT}, I^d, I^C, I_T, I_V$ of model (4) is positive for all $t \geq 0$

3.1 Local stability of the disease-free equilibrium

The (DFE) of the Model (4) is given by $E^0 = (\frac{\Lambda_H}{\mu_H}, 0, 0, 0, 0, 0, \frac{\Lambda_V}{\mu_V}, 0)$ and the local behaviour of the model at or (near) the DFE is determined based on an important quantity, the threshold parameter, the basic reproduction number R_0 [5], which measures the average number of new infections generated by a single infectious individual in a population of completely susceptible individuals. The conditions under which the disease will prevail is determined by this parameter at DFE. In calculating R_0 we use the next generation matrix method [6] and the matrices F and V associated with the next generation method are as given below.

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & ab \\ 0 & \beta & \beta\eta & \beta\sigma & \beta\alpha & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta\zeta & \beta\zeta\eta & \beta\zeta\sigma & \beta\zeta\alpha & 0 \\ \kappa bT & 0 & 0 & \kappa ybT & 0 & 0 \end{pmatrix}$$

and $V = \begin{pmatrix} r_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & r_2 & 0 & 0 & 0 & 0 \\ 0 & -\rho & r_3 & -\xi & 0 & 0 \\ 0 & 0 & 0 & r_4 & 0 & 0 \\ 0 & 0 & -g & 0 & \mu_H & 0 \\ 0 & 0 & 0 & 0 & 0 & \mu_V \end{pmatrix}$

Where $r_1 = q + \delta_M + \mu_H$, $r_2 = \rho + \delta_T + \mu_H + L$, $r_3 = \varpi\delta_T + \mu_H + g$, $r_4 = \xi + \theta\delta_{MT} + \mu_H$, $r_5 = \beta - (\rho + \delta_T + \mu_H + L)$, and $T = \frac{\Lambda_V \mu_H}{\Lambda_H \mu_V}$. The reproduction number
R_{MT} which is the spectral radius of matrix FV^{-1} is given by $R_{MT} = \max\{R_M, R_T\}$. Thus

$$R_{MT} = \max\{\frac{\sqrt{abT\kappa}}{\sqrt{\mu_V(\delta_M + \mu_H + q)}}, \frac{\beta}{r_2} + \frac{\alpha\beta\zeta}{\mu_H} + \frac{\beta\eta\rho}{(r_2)(r_3)} + \frac{\alpha\beta\rho g}{\mu_H r_2 r_3} \quad (5)$$

Where

$R_M = \frac{\sqrt{abT\kappa}}{\sqrt{\mu_V(\delta_M+\mu_H+q)}}$ and

$R_{MT} = \frac{\alpha\beta\zeta}{\mu_H} + \frac{\beta}{\delta_T+\mu_H+\rho+L} + \frac{\beta\eta\rho}{(\mu_H+g+\varpi\delta_T)(\delta_T+\mu_H+\rho+L)} + \frac{\alpha\beta\rho g}{\mu_H(\mu_H+\varpi\delta_T+g)(\delta_T+\mu_H+\rho+L)}$

The reproduction numbers R_M and R_{MT} measure the number of secondary malaria or typhoid infections respectively generated by a single infectious individual in the whole course of her/his infectious period, when introduced in a completely susceptible population [6].

The disease-free equilibrium E^0 of the model (4) is locally asymptotically stable (LAS) if $R_{MT} < 1$ and unstable if $R_{MT} > 1$. $R_{MT} < 1$ generally implies that the disease is eradicated.

3.2 Global stability of the disease-free equilibrium

We determine whether the population can attain global asymptotic stability of the disease-free equilibrium after misdiagnosis of typhoid as malaria using the approach by Castillo-Chavez et al. [2]. We re-write the model (4)

$$\begin{aligned} \frac{dX}{dt} &= F(X,Z), \\ \frac{dZ}{dt} &= G(X,Z), G(X,0) = 0 \end{aligned} \tag{6}$$

Where $X = (S_H, S_V)$ and $Z = (I_M, I_T, I^d, I_{MT}, I^C, I_V)$ in which the components of the column vector $X \in \mathbb{R}^2$ denote the number of uninfected individuals and the components of vector $Z \in \mathbb{R}^6$ denote the number of the infected individuals, including the typhoid bacteria carriers. $Q_0 = (X^*, 0)$ denotes the disease-free equilibrium of this system. The fixed point

$$Q_0 = (X^*, 0) \text{where } X^* = (\frac{\Lambda_H}{\mu_H}, \frac{\Lambda_V}{\mu_V}) \tag{7}$$

is a globally asymptotically stable equilibrium for this system provided $R_{MT} < 1$ (locally asymptotically stable) and the following two conditions satisfied.

$$(I) \text{For } \frac{dX}{dt} = F(X,0), X^* \text{ is globally asymptotically stable (GAS)}\}$$

(II) G(X, Z) = BZ-$\widehat{G}(X,Z), \widehat{G}(X,Z) \geq 0$ for $(X,Z) \in \Omega$

where $B = D_z G(X^*, 0)$ is an M-matrix (the off-diagonal elements of P are non-negative) and Ω is the region where the model makes biological sense.

Proof. We consider

$$F(X,0) = \begin{pmatrix} \Lambda_H - \mu_H S_H \\ \Lambda_V - \mu_V S_V \end{pmatrix}$$

and

$$G(X,Z) = BZ - \widehat{G}(X,Z)$$

where

$$B = \begin{pmatrix} -r_1 & 0 & 0 & 0 & 0 & ab \\ 0 & \beta - r_2 & \beta\eta & \beta\sigma & \beta\alpha & 0 \\ 0 & \rho & -r_3 & \xi & 0 & 0 \\ 0 & 0 & 0 & -r_4 & 0 & 0 \\ 0 & \beta\zeta & \beta\zeta\eta + g & \beta\zeta\sigma & \beta\zeta\alpha - \mu_H & 0 \\ \kappa b & 0 & 0 & \kappa by & 0 & -\mu_V \end{pmatrix}$$

and

$$\widehat{G}(X,Z) = \begin{pmatrix} \widehat{G}_1(X,Z) \\ \widehat{G}_2(X,Z) \\ \widehat{G}_3(X,Z) \\ \widehat{G}_4(X,Z) \\ \widehat{G}_5(X,Z) \\ \widehat{G}_6(X,Z) \end{pmatrix} = \begin{pmatrix} abI_V(1 - \frac{S_H}{N_H}) \\ \beta(I_T + \eta(I^d) + \sigma I_{MT} + \alpha I^C)(1 - \frac{S_H}{N_H})) \\ \gamma\lambda_M I^d \\ -\gamma\lambda_M I^d \\ \beta\zeta(T_T + \eta I^d +_{MT} + \alpha I^C)(1 - \frac{S_H}{N_H}) \\ \kappa b(I_M + \pi I_{MT})(1 - \frac{S_V}{N_H}) \end{pmatrix}$$

We notice that $\widehat{G}(X,Z) < 0$, the conditions in I and II are not satisfied, and hence Q_0 may not be globally asymptotically stable. Backward bifurcation occurs at $R_{MT} = 1$, and an epidemic is most likely to occur.
assuming that there is no misdiagnosis and the typhoid cases are accurately diagnosed and given appropriate treatment $\rho = 0$ then the system (4) is reduced as shown below

$$\begin{aligned} \frac{dS_H}{dt} &= \Lambda_H + qI_M + LI_T - \lambda_M S_H - \lambda_T S_H - \zeta\lambda_T S_H - \mu_H S_H \qquad (8) \\ \frac{dI_M}{dt} &= \lambda_M S_H - \delta_M I_M - \mu_H I_M \\ \frac{dI_T}{dt} &= \lambda_T S_H - LI_T - \delta_T I_T - \mu_H I_T \\ \frac{dI^C}{dt} &= \zeta\lambda_T S_H - \mu_H I^C \qquad (9) \\ \frac{dS_V}{dt} &= \Lambda_V - \mu_V S_V - \lambda_V S_V \\ \frac{dI_V}{dt} &= \lambda_V S_V - \mu_V I_V \end{aligned}$$

We see that when $\rho = 0$ the matrix $\widehat{G}^D(X,Z)$ the matrix without misdiagnosis is given by

$$\widehat{G}(X,Z) = \begin{pmatrix} \widehat{G}_1(X,Z) \\ \widehat{G}_2(X,Z) \\ \widehat{G}_3(X,Z) \\ \widehat{G}_4(X,Z) \\ \widehat{G}_5(X,Z) \\ \widehat{G}_6(X,Z) \end{pmatrix} = \begin{pmatrix} abI_V(1-\frac{S_H}{N_H}) \\ \beta(I_T+\sigma I_{MT}+\alpha I^C)(1-\frac{S_H}{N_H})) \\ 0 \\ 0 \\ \beta\zeta(T_T+_{MT}+\alpha I^C)(1-\frac{S_H}{N_H}) \\ \kappa b(I_M+\pi I_{MT})(1-\frac{S_V}{N_H}) \end{pmatrix}$$

In this case ($\widehat{G}^D(X,Z) > 0$), this means there is global stability. Hence we have the following theorem: In the event of accurate diagnosis and prompt treatment, the disease-free equilibrium is globally asymptotically stable. The disease is eradicated within the larger population of the secondary infectives.

3.3 Sensitivity Analysis of (R_{MT})

To investigate the potential impact of misdiagnosis on disease progression and transmission, we carry out sensitivity analysis of the reproduction numberR_{MT}, in order to determine the parameters which have high impact on R_{MT} that should be targeted for intervention strategies. In order to determine how best to reduce human mortality and morbidity due to typhoid, it is necessary to know the relative importance of the different factors responsible for it's spread and prevalence. The sensitivity indices of the reproduction number are computed using the approach by Chitnis [3] as follows: differentiating R_{MT} partially with respect to ρ yields

$$\urcorner^{R_{MT}} = \frac{\partial R_{MT}}{\partial \rho}\frac{\rho}{R_{MT}} = \beta\ln(\delta_T+\mu_H+\rho+L) + \frac{\beta\eta(\mu_H+g+\varpi\delta_T)(\delta_T+\mu_H+\rho+L)}{(\mu_H+g+\varpi\delta_T)(\delta_T+\mu_H+\rho+L)} + \frac{\alpha\beta g(\mu_H(\mu_H+\varpi\delta_T+g)(\delta_T+\mu_H+\rho+L)}{\mu_H(\mu_H+\varpi\delta_T+g)(\delta_T+\mu_H+\rho+L)}. \quad (10)$$

Similarly we compute sensitivity indices of the reproduction number R_{MT} to the parameters g, ζ and L and compare the results to find out the most sensitive parameter. The positive sign in (10) indicates that there is an expected increase in the rate of new typhoid infections when misdiagnosis is scaled up. There is similar occurrence for g and ζ
. The sensitivity indices to the parameters and the values of the respective parameters used are as given in Table 1

parameters	value	sensitivity index
ρ	$0.08\,\text{day}^{-1}$	0.7914
L	$0.00075\,\text{day}^{-1}$	-2.709$\times 10^{-2}$
g	$0.1\,\text{day}^{-1}$	0.6351
ζ	$0.1\,\text{day}^{-1}$	0.4945

Table 1: Sensitivity indices.

The most sensitive parameter is the misdiagnosis rate ρ. This suggests that accurate diagnosis in treatment of typhoid has positive impact in controlling typhoid in the community. Reducing the rate of misdiagnosis through laboratory tests would have the largest effect on typhoid transmission. It can also be noted that the moment ρ increases or decreases, g also increases or decreases considerably.

4 Summary

The DFE is stable if $R_{MT} < 1$ and unstable if $R_{MT} > 1$, but it is shown that in the presence of misdiagnosis it is not possible to eradicate malaria and typhoid despite $R_{MT} < 1$. In the event of the absence of misdiagnosis ($\rho = 0$), $R_{MT} = \max\{R_M^0, R_{MT}^0\} = \max\{\frac{\sqrt{abT\kappa}}{\sqrt{\mu_V(\delta_M+\mu_H+q)}}, \frac{\alpha\beta\zeta}{\mu_H} + \frac{\beta}{(\delta_T+\mu_H+L)}\}$. It is noted that $R_{MT}^0 \ll R_{MT}$ which implies that the right diagnosis can greatly reduce the burden of typhoid fever[4]. R_{MT} is also greatly dependent on ζ and g, the probabilities of becoming a typhoid bacteria carrier. In the case of the right diagnosis g is greatly reduced and consequently I^C is reduced [7]. In the absence of carriers $R_{MT}^{-C} = \frac{\beta}{(\delta_T+\mu_H+L)} \ll R_{MT}$. In the event of no misdiagnosis at all, which may not be practical in real life situation, $R_{MT} = \frac{\beta}{(\delta_T+\mu_H+L)}$. We observe that $R_{MT} \to 0$ since $L \to \infty$ and $\beta \to 0$, a situation of no typhoid in the population. An effective typhoid vaccine would ensure that during contact of a vaccinated susceptible with an infective, more so, a carrier, $\beta \to 0$ and hence $R_{MT} \to 0$. The two reproduction numbers are the same, which is an indication that both misdiagnosis and carriers increase transmission of typhoid equally.

We observe that misdiagnosis of typhoid as malaria increases the transmission of typhoid fever by increasing the rate of contact with salmonella typhi and the number of typhoid bacteria carrier. Carriers are a group of people who in our setup, we are not able to associate them with typhoid bacteria and this greatly increases their chances of spreading the bacteria. Untreated typhoid kills 20 percent of those it infects and many who survive become carriers for life e.g. typhoid Mary who infected several people with typhoid before it was

discovered that she was a carrier [8]. This explains why increase in carriers increases the population of those with typhoid. Carriers cause the greatest number of infection especially in the rural setup where there are poor sanitation systems and people use largely untreated water from wells and ponds.

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