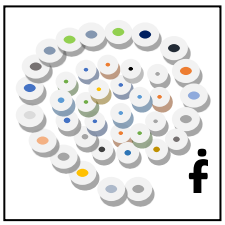

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Sensitivity analysis of the parameters of a co-infection model of Malaria and Dengue Fever disease

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Abstract

In the paper, we present a mathematical model of malaria and dengue fever co-infection. We state the Disease Free and Endemic Equilibrium of the model equations. We compute the reproduction number using the next generation matrix method. Sensitivity analysis of the reproduction number was carried out. Our results shows that the disease vectors death rate is the most sensitivity parameters which further imply that eliminating or reducing the disease vector is the most effective control measure in controlling the transmission of malaria-dengue co-infection.

***Keywords*:** Malaria; Dengue Fever; co-infection; sensitivity analysis

1 Introduction

Malaria and Dengue Fever (DF) are common vector-borne diseases that pose major public health challenges [1, 2].

Malaria is vector-borne disease caused by protozoan parasites belonging to Plasmodium species. The parasites are transmitted through the bites of an infected female Anopheles mosquitoes [3, 4, 5]. According to the 2018 World Malaria Report, 219 million cases of malaria occurred globally in 2017 resulting into 435, 000 death. African region having the highest cases of 92%, South-East Asia 5% and Eastern Mediterranean 2%. Nigeria, Democratic Republic of Congo (DRC), Mozambique, India and Uganda are the countries with almost half of the malaria reported cases globally. Nigeria, DRC, Burkina Faso, United Republic of Tanzania, Sierra Leone, Niger and India has more than half of malaria recorded death.

Dengue Fever (DF) is a viral infection transmitted by the bites of an infected Aedes aegypti mosquitoes. It is prevalent in subtropical and tropical regions. The disease is threatening about 40% of the world's population [6, 7]. Over 3 billion people are at risk of been infected with Dengue fever

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annually in over 125 endemic countries, and it is estimated to cause the death of about 10,000 people annually. Factors that account for the global transmission of dengue includes rapid population growth, increased international travel, and development of the agricultural sector, unplanned urbanization and global climate change. Ineffective mosquito control and inadequate health facilities also contribute to the global transmission [8, 9].

Dengue Fever and Malaria co-infection is rising in the tropics causing high morbidity and mortality globally [10]. The co-infection of Dengue Fever and Malaria is possible in an area where dengue and malaria vectors co-exist. The co-infection was first reported in 2005. Dengue Fever and Malaria co-infection exhibit clinical features of both dengue and malaria mono-infection resulting in misdiagnosis. Dengue and Malaria co-infection has been reported in 44 locations spread across 20 countries. The co-infection varies ranging between 0.1 – 23 % from south Asia, 0.01 – 9% from Africa, 0.5 – 2.5 % from South East Asia and 1 – 3 % from South America [11]. The high rate of the mobility of today's population and increased activities associated with movement of goods and services from one location to another is likely to increase the incidences of dengue and malaria co-infection [12].

Sensitivity Analysis is used to determine how a model response to changes in the value of the parameters of the model. Sensitivity Analysis is extremely important for mathematical models. It studies the variation of a model caused by variations in the inputs [13]. Atokolo and Omale [13] investigated the sensitivity analysis of typhoid fever transmission, the result shows that increase in enlightenment, campaign will lead to reduction in prevalence. Sirajo *et al.* (14) carried out a sensitivity analysis of parameters of Hepatitis B Model, the result revealed that vaccination, condom use and reduced-average sexual partner can reduce and control the spread of Hepatitis B. Marsudi *et al.* [15] studied the sensitivity analysis of the parameters of HIV/AIDS model with condom campaign and Antiretroviral Therapy (ARV).

In this study, analyze the parameters of the co-infection model of malaria-dengue fever to determine which is most sensitive.

2 Model Formulation

In this model, the total human population at time t denoted by N_h is divided into eight sub-classes which are susceptible humans (S_h), individuals exposed to malaria only (E_{hm}), individuals infected with malaria only (I_{hm}), individuals exposed to dengue fever only (E_{hd}), individuals infected with only dengue fever (I_{hd}), individuals exposed to malaria and dengue fever co-infection (E_{md}), individuals infected with malaria and dengue fever co-infection (I_{md}), individuals that recovered from malaria and dengue fever (R_h). The vector population includes the Malaria Parasite non-carrier vectors (S_m), Malaria parasite carrier vectors (I_m), Dengue virus non-carrier vectors (S_d) and Dengue fever carrier vectors (I_d).

2.1 Model Assumptions

The following Assumptions are made in formulating the model:

1. Recruitment into the population is into the susceptible class only
2. The recovered class includes those who recover from malaria only, dengue only and co-infection of both
3. Those who recover from malaria can be re-infected with malaria or dengue
4. Both the Exposed and Infected classes are involved in the transmission of the diseases.

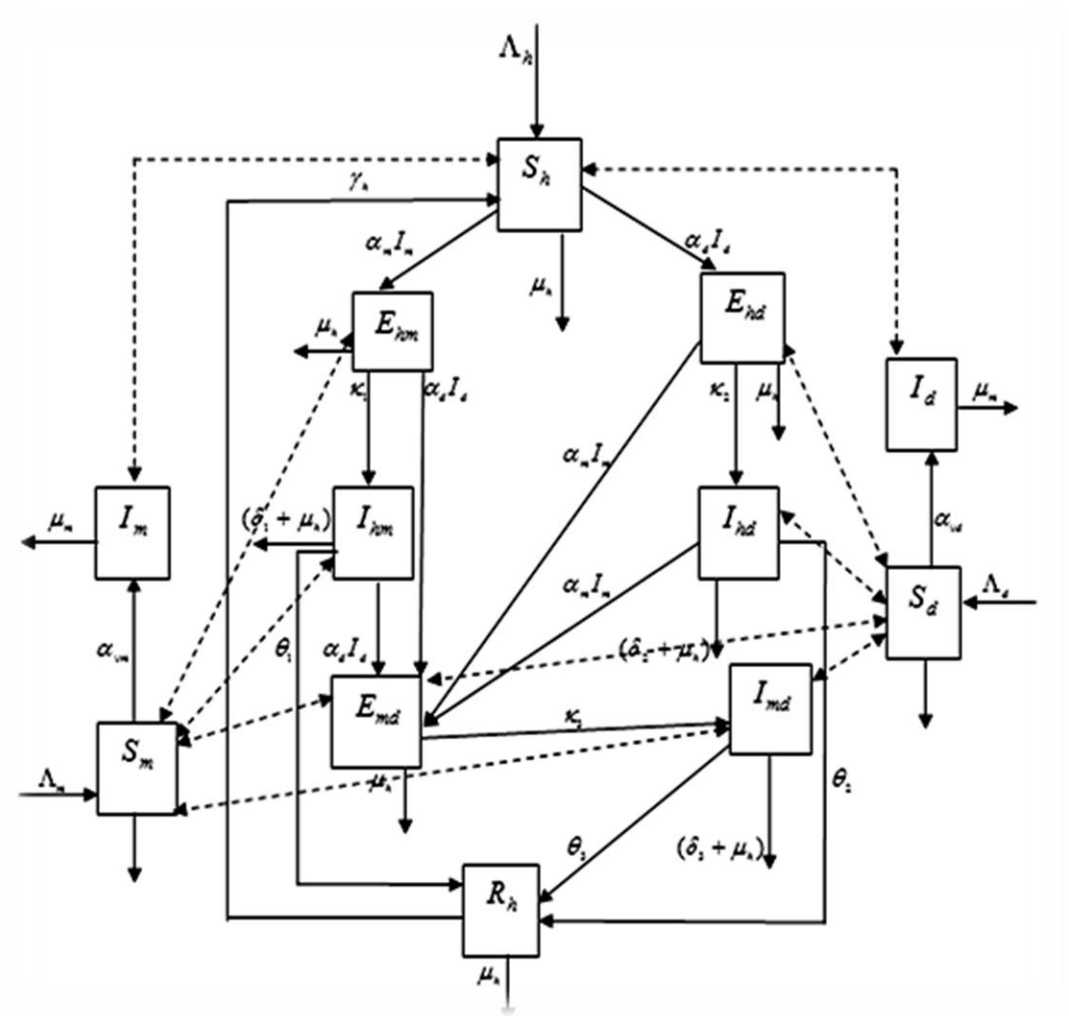

Figure 2.1: Schematic Diagram of the Model

Based on the assumptions, the equations governing the co-infection dynamics is given as,

$$\frac{dS_h}{dt} = \Lambda_h + \gamma_h R_{hm} - (\alpha_d I_d + \alpha_m I_m) S_h - \mu_h S_h$$

$$\frac{dE_{hm}}{dt} = \alpha_m I_m S_h - (\alpha_d I_d + \kappa_1 + \mu_h) E_{hm}$$

$$\frac{dI_{hm}}{dt} = \kappa_1 E_{hm} - (\alpha_d I_d + \delta_1 + \theta_1 + \mu_h) I_{hm}$$

$$\frac{dE_{hd}}{dt} = \alpha_d I_d S_h - (\alpha_m I_m + \kappa_2 + \mu_h) E_{hd}$$

$$\frac{dI_{hd}}{dt} = \kappa_2 E_{hd} - (\alpha_m I_m + \delta_2 + \theta_2 + \mu_h) I_{hd}$$

$$\frac{dE_{md}}{dt} = \alpha_d I_d E_{hm} + \alpha_d I_d I_{hm} + \alpha_m I_m E_{hd} + \alpha_m I_m I_{hd} - (\kappa_3 + \mu_h) E_{md}$$

$$\frac{dI_{md}}{dt} = \kappa_3 E_{md} - (\delta_3 + \theta_3 + \mu_h) I_{md}$$

$$\frac{dR_{hm}}{dt} = \theta_1 I_{hm} + \theta_2 I_{hd} + \theta_3 I_{md} - (\gamma_h + \mu_h) R_{hm}$$

$$\frac{dS_m}{dt} = \Lambda_m - \alpha_{vm}(E_{hm} + I_{hm} + E_{md} + I_{md}) S_m - \mu_m S_m$$

$$\frac{dI_m}{dt} = \alpha_{vm}(E_{hm} + I_{hm} + E_{md} + I_{md}) S_m - \mu_m I_m$$

$$\frac{dS_d}{dt} = \Lambda_d - \alpha_{vd}(E_{hd} + I_{hd} + E_{md} + I_{md}) S_d - \mu_d S_d$$

$$\frac{dI_d}{dt} = \alpha_{vd}(E_{hd} + I_{hd} + E_{md} + I_{md}) S_d - \mu_d I_d$$

Table 1: Model Variables

Symbols	Description
S_h	Susceptible Humans
E_{hm}	Exposed Humans with Malaria
I_{hm}	Humans infected with Malaria only
E_{hd}	Exposed Humans with Dengue Fever
I_{hd}	Humans infected with Dengue Fever only
E_{md}	Exposed Humans jointly infected with Malaria and Dengue Fever
I_{md}	Humans jointly infected with Malaria and Dengue Fever
R_h	Humans Recovered from Malaria and Dengue Fever
S_m	Malaria Parasite carrier vectors
I_m	Malaria Parasite non-carrier vectors
S_d	Dengue virus non-carrier vectors
I_d	Dengue virus carrier vectors

Table 2: Model Parameters

Symbols	Description
Λ_h	Recruitment rate of Human Population
Λ_m	Recruitment rate of Malaria Parasite Vectors
Λ_d	Recruitment rate of Dengue Virus Vectors
θ_1	Recovery rate for Humans infected with Malaria only
θ_2	Recovery rate for Human infected with Dengue only
θ_3	Recovery rate for Human jointly infected with Malaria and Dengue
γ_h	Rate at which recovered becomes susceptible
κ_1	Rate at which E_{hm} becomes I_{hm}
κ_2	Rate at which E_{hd} becomes I_{hd}
κ_3	Rate at which E_{md} becomes I_{md}
α_m	Transmission rate from Human to Malaria Parasite Vectors
α_d	Transmission rate from Human to Dengue Virus Carrier Vectors
α_{vm}	Probability for Malaria Parasite Vectors to be infected
α_{vd}	Probability for Dengue Virus Vectors to be infected
δ_1	Malaria Induced Death

δ_2	Dengue Induced Death
δ_3	Co-infection Induced Death
μ_h	Natural death rate for Humans
μ_m	Natural death rate of Malaria Parasite Vectors
μ_d	Natural death rate of Dengue Virus Vectors

3 Model Analysis

3.1 Model Equilibria Points

The Disease-Free Equilibrium (DFE) of the co-infection Model is given by

$$\varepsilon_0 = \left(S_h^0, E_{hm}^0, I_{hm}^0, E_{hd}^0, I_{hd}^0, E_{md}^0, I_{md}^0, R_{hm}^0, S_m^0, I_m^0, S_d^0, I_d^0\right)$$
$$= \left(\frac{\Lambda_h}{\mu_h}, 0,0,0,0,0,0,0, \frac{\Lambda_m}{\mu_m}, 0, \frac{\Lambda_d}{\mu_d}, 0\right)$$

while the Endemic Equilibrium point (EEP) is given by

$$\varepsilon_E = \left(S_h^*, E_{hm}^*, I_{hm}^*, E_{hd}^*, I_{hd}^*, E_{md}^*, I_{md}^*, R_{hm}^*, , S_m^*, I_m^*, S_d^*, I_d^*\right) =$$
$$\left(\begin{array}{c}
\frac{Q_6}{Q_4+Q_5}, \frac{\alpha_m I_m Q_6}{(\alpha_d I_d+\eta_1)(Q_4+Q_5)}, \frac{\kappa_1 \alpha_m I_m Q_6}{(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)(Q_4+Q_5)}, \\
\frac{\alpha_d I_d Q_6}{(\alpha_m I_m+\eta_2)(Q_4+Q_5)}, \frac{\kappa_2 \alpha_d I_d Q_6}{(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2)(Q_4+Q_5)}, \\
\frac{\alpha_d I_d \alpha_m I_m Q_3 Q_6}{\eta_3(Q_4+Q_5)}, \frac{\alpha_d I_d \alpha_m I_m \kappa_3 Q_3 Q_6}{z_3 \eta_3(Q_4+Q_5)}, \frac{\Lambda_h Q_7}{(Q_4+Q_5)}, \\
\frac{\Lambda_m(\alpha_d I_d+\eta_1)(Q_4+Q_5)}{\alpha_{vm}\alpha_m I_m Q_1 Q_6+\mu_m(\alpha_d I_d+\eta_1)(Q_4+Q_5)}, \\
\frac{\Lambda_m \alpha_{vm}\alpha_m I_m Q_1 Q_6}{\mu_m(\alpha_{vm}\alpha_m I_m Q_1 Q_6+\mu_m(\alpha_d I_d+\eta_1)(Q_4+Q_5))}, \\
\frac{\Lambda_d(\alpha_m I_m+\eta_2)(Q_4+Q_5)}{\alpha_{vd}\alpha_d I_d Q_2 Q_6+\mu_d(\alpha_m I_m+\eta_2)(Q_4+Q_5)}, \\
\frac{\Lambda_d \alpha_{vd}\alpha_d I_d Q_2 Q_6}{\mu_d(\alpha_{vd}\alpha_d I_d Q_2 Q_6+\mu_d(\alpha_m I_m+\eta_2)(Q_4+Q_5))}
\end{array}\right)$$

where

$$Q_1 = \left(\left(1+\frac{\kappa_1}{(\alpha_d I_d + z_1)}\right) + \frac{\alpha_d I_d}{\eta_3}\left(\frac{(\alpha_d I_d+\rho_1)(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2) + (\alpha_m I_m+\rho_2)(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)}{(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2)} \right)\left(1+\frac{\kappa_3}{z_3}\right) \right)$$

$$Q_2 = \left(\left(1+\frac{\kappa_2}{(\alpha_m I_m + z_2)}\right) + \frac{\alpha_m I_m}{\eta_3}\left(\frac{(\alpha_d I_d+\rho_1)(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2) + (\alpha_m I_m+\rho_2)(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)}{(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2)} \right)\left(1+\frac{\kappa_3}{z_3}\right) \right)$$

$$Q_3 = \left(\frac{(\alpha_d I_d+\rho_1)(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2) + (\alpha_m I_m+\rho_2)(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)}{(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2)} \right)$$

$$Q_4 = z_3\eta_3\mu_h\left(\frac{(\alpha_d I_d+\alpha_m I_m+\mu_h)(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)}{(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2)} \right)$$

$$Q_5 = \gamma_h\left(\frac{z_3\eta_3(\alpha_d I_d+\alpha_m I_m+\mu_h)(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)(\alpha_m I_m+z_2)}{(\alpha_m I_m+\eta_2) - \left(\begin{array}{c} \theta_1\kappa_1\alpha_m I_m z_3\eta_3(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2) \\ +\theta_2\kappa_2\alpha_d I_d z_3\eta_3(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1) \\ +\theta_3\kappa_3\alpha_d I_d\alpha_m I_m Q_3(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1) \\ (\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2) \end{array} \right)} \right)$$

$$Q_6 = \Lambda_h z_3\eta_3(\gamma_h+\mu_h)(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2)$$

$$Q_7 = \theta_1\kappa_1 z_3\eta_3\alpha_m I_m(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2) + \theta_2\kappa_2 z_3\eta_3\alpha_d I_d(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)$$
$$+\theta_3\kappa_3\alpha_m I_m\alpha_d I_d(\alpha_d I_d+z_1)(\alpha_d I_d+\eta_1)(\alpha_m I_m+z_2)(\alpha_m I_m+\eta_2)$$

3.2 Reproduction Number (R_0)

We apply the next generation method to compute the Reproduction Number. This is the expected number of secondary infections produced when one infected individual is introduced into a susceptible population. So $R_0 = \rho\left(FV^{-1}\right)$ where F is the matrix of new infections and V is the matrix consisting of the transition terms. The matrices are given by

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \alpha_m \frac{\Lambda_h}{\mu_h} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha_d \frac{\Lambda_h}{\mu_h} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \alpha_{vm} \frac{\Lambda_m}{\mu_m} & \alpha_{vm} \frac{\Lambda_m}{\mu_m} & 0 & 0 & \alpha_{vm} \frac{\Lambda_m}{\mu_m} & \alpha_{vm} \frac{\Lambda_m}{\mu_m} & 0 & 0 \\ 0 & 0 & \alpha_{vd} \frac{\Lambda_d}{\mu_d} & \alpha_{vd} \frac{\Lambda_d}{\mu_d} & \alpha_{vd} \frac{\Lambda_d}{\mu_d} & \alpha_{vd} \frac{\Lambda_d}{\mu_d} & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} \eta_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\kappa_1 & z_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \eta_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\kappa_2 & z_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \eta_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\kappa_3 & z_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \mu_m & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mu_d \end{pmatrix}$$

So

$$\rho\left(FV^{-1}\right) = R_0 = \max\{R_{0m}, R_{0d}\},$$

where

$$R_{0m} = \sqrt{\frac{\Lambda_h \Lambda_m \alpha_m \alpha_{vm} (z_1 + \kappa_1)}{\eta_1 z_1 \mu_h \mu_m^2}} \quad \text{and}$$

$$R_{0d} = \sqrt{\frac{\Lambda_h \Lambda_d \alpha_d \alpha_{vd} (z_2 + \kappa_2)}{\eta_2 z_2 \mu_h \mu_d^2}}.$$

4 Sensitivity Analysis

In this section, sensitivity analysis is carried out to identify the most influential parameter(s) on the reproduction number. The techniques in [16] is applied. Given a parameter, say ξ the sensitivity index of R_0 with respect to ξ is given by

$$\mathrm{K}_{\xi}^{R_0} = \frac{\partial R_0}{\partial \xi} \frac{\xi}{R_0}.$$

Since $R_0 = \max\{R_{0m}, R_{0d}\}$, we obtain the analysis for R_{0m} and R_{0d} separately, using values in Table 3 below.

Table 3: Parameter Values

Symbols	Values	Source
θ_1	0.99	Calculated
θ_2	2.5	Garba *et al.* (2008)
κ_1	0.058	Olaniyi *et al.* (2018)
κ_2	0.074	Assumed
α_m	0.75	Olaniyi and Obabiyi (2013)
α_d	0.833	Garba *et al.* (2008)
α_{vm}	0.5	Labadin *et al.* (2009)
α_{vd}	0.09	Garba *et al.* (2008)
δ_1	0.015	Calculated
δ_2	0.36	James and Eguda (2017)
μ_h	0.0116	Calculated
μ_m	0.75	Labadin *et al.* (2009)
μ_d	0.365	Blayneh *et al.* (2009)

The Sensitivity indices is given in Table 4 below.

Table 4: Sensitivity Indices

Parameter	Sensitivity Index
R_{0m}	Basic Reproduction number of Malaria
α_m	1.000000001
α_{vm}	1.000000000
δ_1	-0.002632231
θ_1	-0.249184537
κ_1	-0.561160644
μ_h	-1.187022586
μ_m	-2.00000000
R_{0d}	Basic Reproduction number of Dengue
α_d	1.000000000
α_{vd}	1.000000000
δ_2	-0.003149462
θ_2	-0.021871270
κ_2	-0.839363765
μ_h	-1.135615500
μ_d	-2.000000000

5 Discussion and Conclusion

As outline in Table 4 the parameters have negative or positive effects as indicated by the signs. Parameters with negative signs $(\delta_1, \delta_2, \theta_1, \theta_2, \kappa_1, \kappa_2, \mu_h, \mu_m, \mu_d)$ when increased with other parameters remaining constant will reduce the value of R_0. Otherwise, increasing any of the indices with positive signs will increase the value of the reproduction number (R_0). It is observed that the most sensitive parameters are the vectors death rate (μ_m, μ_d). This implies that control strategies that concentrate on eliminating or reducing the disease vectors will be most effective in reducing the transmission of malaria and dengue fever disease.

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