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Mathematical Model on Plasmodium knowlesi

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Abstract
Human beings are the natural hosts for four species of *Plasmodium* (*Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae* and *Plasmodium ovale*), which is the causative agent of malaria. *Plasmodium knowlesi,* a simian malaria parasite, is now recognized as the fifth cause of human malaria and can lead to fatal infections in humans. We present a mathematical model on *plasmodium knowlesi* for human malaria by taking three populations of humans, mosquitoes and monkeys. We formulated $S_HE_HI_HR_H$ model for human population, $S_mE_mI_m$ model for mosquito population and $S_ME_MI_MR_M$ model for monkey population. We define a basic reproductive number R_0 and equilibrium points for our model. We prove that the disease-free equilibrium is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. Extensive numerical simulations are carried out to establish the analytical results with real parametric values and sensitivity analysis of basic reproduction number is also carried out with the transmission probability for malaria in all three population of humans, mosquitoes and monkeys. Finally, the analysis of inoculation on the infected human and monkey population is carried out.

Keywords: Plasmodium Knowlesi, Basic reproduction rate, stability analysis, simulation.

1. Introduction

Plasmodium knowlesi was first recognized in India from a long-tailed macaque imported from Singapore in 1931. It can infect humans, which was first identified in 1932, when Knowles and Das Gupta successfully transmitted the parasite to two human volunteers by blood passages from infected macaques[1]. In 1965, the first human infection of P. knowlesi was identified in an American army surveyor who had infected with the disease during working in the forest in the state of Pahang, Malaysia [2]. It was followed by a presumptive case recognized from the state of Johor, Malaysia, which is nearby to the island of Singapore [3]. In 2004, Human infections were rare, till a large amount of humans were infected with Plasmodium knowlesi identified by nested polymerase chain reaction detected in Sarawak, Malaysian Borneo [4]. Since then, cases of P. knowlesi infections in humans have been identified in another parts of Malaysia, China, Thailand, Philippines, and Singapore [5,6,7, 8, 9], resulting in plasmodium knowlesi being identified as the first Plasmodium species concerned to zoonotic disease. In Singapore, the first recognized P. knowlesi infected human found in 2007 and worked as a soldier in the Singapore military who had no significant travel experienced and skilled in a restricted-access forested area in Singapore [9]. Plasmodium knowlesi infections have also been recognized from European travelers returning from endemic countries [10,11].

Theoretically there are four modes of transmission: from an infected monkey to another monkey, from an infected monkey to a human, from an infected human to another human and from an infected human back to a monkey [12].

Initial studies conducted in Malaysia identified Anopheles mosquito as the vector of Plasmodium knowlesi but since this mosquito is not attracted to humans, feeds mainly on monkeys and is found only in the deep forest [13,14]. In the Kapit district of Sarawak recognized A. latens, which belongs to the Leucosphyrus mosquitoes group, as the main natural vector of Plasmodium knowlesi for both monkeys and humans [15,16,17]. The Anopheles leucosphirus group of mosquitoes has been found in South-western India, eastward to Southern China, Taiwan, mainland Southeast Asia, Indonesia and Philippines [18]. Experimental laboratory studies carried out and found that A. quadrimaculatus was naturally resistant to the parasite while A. balabacensis emerged as the most efficient vector producing more than one thousand sporozoites and inducing infection in monkeys after a period of 7-8 days [12].

The long-tailed and the pig-tailed macaque found in South-east Asian countries are the two principal natural monkey hosts of Plasmodium knowlesi [19,20,21], however the parasite can also be detected naturally in banded leaf monkey [22]. In its natural hosts, Plasmodium knowlesi infection generally induces a mild and transient disease with chronic, low-grade parasitemia [23,24]. M. fascicularis is found in a large scale of habitats from Brunei, Cambodia, Indonesia, Southern Thailand and Peninsular Malaysia to Sumatra, Java, Borneo, the Philippines, Singapore and southern Viet Nam. It has been expected that long-tailed macaques have the third most widespread geographical distribution among primates after humans and rhesus macaques [25].

A recent survey conducted on 108 wild-macaques in the Kapit Division of Sarawak showed a very high prevalence of malaria parasites (94%) detected by nested polymerase chain reaction [26]. Plasmodium knowlesi circulation among macaques in Thailand seems to be lower, with prevalence of 5.6% observed among long-tailed and of 2.3% among pig-tailed [27].

The most common test results and comparisons with plasmodium vivax and plasmodium falciparum in 107 knowlesi patients at Kapit Hospital of Sarawak are shown in Appendix 1 [28].

In comparison with complications of severe Plasmodium falciparum malaria inferred from studies of imported malaria patients with severe Plasmodium knowlesi malaria were notable for the absence of cerebral malaria and severe anemia (see Appendix 2) [29,30]. However, in a single autopsy study performed on a 40 year-old man who died for Plasmodium knowlesi malaria, sequestered parasitized erythrocytes were observed in the small vessels of brain, heart and kidney but brain section were notably negative for immuno-histochemistry markers of intracellular adhesion molecule-1 suggesting but not showing a different procedure from falciparum cerebral malaria using blood from 5 patients with polymerase chain reaction confirmed Plasmodium knowlesi malaria experimentally found that infected erythrocytes were capable to combine the inducible endothelial receptor [31,32]. It is also important fact that near two-third of patients with severe Plasmodium knowlesi malaria had more than one WHO criterion (see Appendix 2). Up to now 19 patients with Plasmodium knowlesi malaria have been reported with a fatal outcome and the case fatality rate inferred by the three largest studies is 3.4% [28,33,34].

2. **Model description and Formulation**:

In 1911, Mathematical modeling of malaria has started with the model developed by Ross [35], and the most important extensions of malaria model are described in a book, written by Macdonald [36]. Another important extension of the malaria models was the inclusion of acquired immunity proposed by Dietz, Molineaux and Thomas [37]. Another extension work on acquired immunity in malaria has been conducted by Aron [38] and Bailey [39]. Anderson and May [40], Aron and May [41], and Nedelman [42] have given some excellent reviews on the mathematical modeling of malaria. Some recent papers have also added environmental effects [43, 44], the spread of resistance to drugs [45] and the evolution of immunity [46].

In our model, we divides the human population into four classes, which are as follows: susceptible class, S_H ; exposed class E_H; infectious class I_H; and recovered class, R_H. Humans enter the susceptible class S_H by birth rate b_H and immigration rate e. When an infectious mosquito bites a susceptible human, there is some finite probability that the parasite enters to human body and that human moves to the exposed class. The parasite then travels to the liver of human body, where it develops into its next life stage. After a certain period of time, the parasite goes to the blood stream and indicating the clinical beginning of malaria. In our model, human from the exposed class go to the infected class at a rate γ. After certain time, the infectious humans go to the recovered class at a rate α. Then, the recovered class of humans has some immunity to the disease and due to that they do not get clinically sick, but they have still low levels of parasite in their blood and can infect the mosquitoes. After certain period of time, they lose their immunity and go back to the susceptible class at a constant rate r_H. Humans leave the population through emigration rate e, natural death rate d, and a disease-induced death rate d_H.

We divide the mosquito population into three classes, which are as follows: susceptible class S_m, exposed class E_m, and infected class I_m. Female mosquitoes enter the susceptible class by birth rate b_m. The parasite enters the mosquito with some probability when the mosquito bites an infectious human or a recovered human and the mosquito moves from the susceptible to the exposed class. We assume the probability of transmission of infection from a recovered human is much lower than that from an infectious human. After certain period of time, the parasite develops into sporozoites and goes to the salivary glands of mosquito, then the mosquito moves from the exposed class to the infected class at a rate μ. The mosquito remains infectious for life time. Mosquitoes go out from the population through natural death rate d_m [1].

We divides the monkey population into four classes, which are as follows: susceptible class S_M, exposed class E_M; infected class I_M; recovered class R_M. Epidemic transmission of monkey population is same as human population. We assumed that transmission rate from infected class to recovered class is very less in monkey population.

In our model, the total number of bites depends on the population sizes of human, monkey and mosquito. Human migration is present in all over the world and plays an important role in the epidemiology of diseases, including malaria.

The state variables (Table 1) and parameters (Table 2) for the malaria model (Figure 1) satisfy the modal equations.

Table 1

The state variables for the malaria model.
S_H: Number of susceptible humans
E_H: Number of exposed humans
I_H: Number of infectious humans
R_H: Number of recovered (immune and asymptomatic, but slightly infectious) humans
S_m: Number of susceptible mosquitoes
E_m: Number of exposed mosquitoes
I_m: Number of infectious mosquitoes
N_H: Total human population
N_m: Total mosquito population
N_M: Total human population
S_M: Number of susceptible monkeys
E_M: Number of exposed monkeys
I_M: Number of infectious monkeys
R_M: Number of recovered (immune and asymptomatic, but slightly infectious) monkeys

Table 2

The parameters for the malaria model.

β_{mH}: Probability of transmission of infection from an infectious mosquito to a susceptible human, given that a contact between the two occurs.

β_{Hm}: Probability of transmission of infection from an infectious human to a susceptible mosquito, given that a contact between the two occurs.

β_{mM}: Probability of transmission of infection from an infectious mosquito to a susceptible monkey, given that a contact between the two occurs.

β_{Mm}: Probability of transmission of infection from an infectious monkey to a susceptible mosquito, given that a contact between the two occurs.

e : Immigration rate of humans.

e_m :Immigration rate of mosquitoes.

b_H : birth rate of humans.

b_m : birth rate of mosquitoes.

b_M : birth rate of monkeys.

γ: rate of progression of humans from the exposed state to the infectious state

μ: rate of progression of mosquitoes from the exposed state to the infectious state.

η: rate of progression of monkeys from the exposed state to the infectious state

α: recovery rate for humans from the infectious state to the recovered state

ξ: recovery rate for monkeys from the infectious state to the recovered state

d_H: disease-induced death rate for humans.

r_H : rate of transmission from recovered class to Susceptible class for humans.

r_M : rate of transmission from recovered class to Susceptible class for monkeys.

d : natural death rate for humans.

d_m: natural death rate for mosquitoes.

d_M: natural death rate for monkeys.

d_e: disease-induced death rate for monkeys.

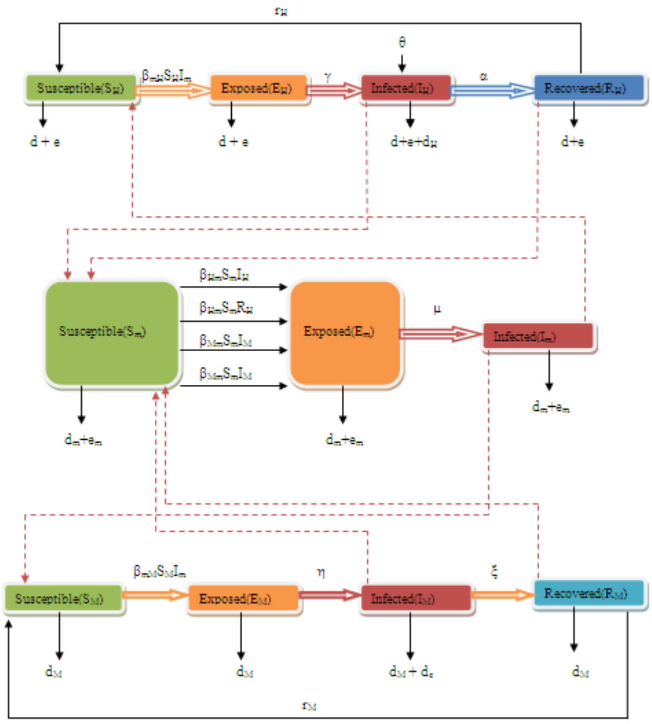

Figure 1: Schematic diagram for the flow of Plasmodium Knowlesi.

These are the following model equations of our model:

$$\frac{dS_H}{dt} = b_H N_H - \beta_{mH} S_H I_m - (d+e)S_H + r_H R_H$$

$$\frac{dE_H}{dt} = \beta_{mH} S_H I_m - (d+e+\gamma)E_H$$

$$\frac{dI_H}{dt} = \gamma E_H - (d+e+d_H+\alpha-\theta)I_H$$

$$\frac{dR_H}{dt} = \alpha I_H - (d+e+r_H)R_H$$

$$\frac{dS_m}{dt} = b_m N_m - \beta_{Hm} S_m (I_H + R_H) - (d_m + e_m)S_m - \beta_{Mm} S_m (I_M + R_M)$$

$$\frac{dE_m}{dt} = \beta_{Hm} S_m (I_H + R_H) + \beta_{Mm} S_m (I_M + R_M) - (d_m + e_m + \mu)E_m$$

$$\frac{dI_m}{dt} = \mu E_m - (d_m + e_m) I_m$$

$$\frac{dS_M}{dt} = b_M N_M - \beta_{mM} S_M I_m - d_M S_M + r_M R_M$$

$$\frac{dE_M}{dt} = \beta_{mM} S_M I_m - (d_M + \eta)E_M$$

$$\frac{dI_M}{dt} = \eta E_M - (d_M + d_e + \xi) I_M$$

$$\frac{dR_M}{dt} = \xi I_M - (d_M + r_M) R_M$$

3. Stability analysis of the model

Finding equilibrium states by setting the right hand side of all the model equations equal to zero, and then we obtain two equilibrium states:

(i) Disease free equilibrium state: E_0 = (1,0,0,0,1,0,0,1,0,0,0)

(ii) Endemic equilibrium state : $E_1 = (S_H^*, E_H^*, I_H^*, R_H^*, S_m^*, E_m^*, I_m^*, S_M^*, E_M^*, I_M^*, R_M^*)$,

Where

$$S_H^* = \frac{b_H N_H + r_H R_H^*}{\beta_{mH} I_m^* + d + e}, E_H^* = \frac{\beta_{mH} S_H^* I_m^*}{(d + e - \gamma)},,$$

$$I_H^* = \frac{\gamma E_H^*}{(d+e+d_H+\alpha-\theta)}, R_H^* = \frac{\alpha I_H^*}{(r_H+d+e)},$$

$$S_m^* = \frac{b_m N_m}{\beta_{Hm}(I_H^*+R_H^*)+\beta_{Mm}(I_M^*+R_M^*)+d_m+e_m},$$

$$E_m^* = \frac{\beta_{Hm} S_m^*(I_H^*+R_H^*)+\beta_{Mm} S_m^*(I_M^*+R_M^*)}{(\mu+d_m+e_m)},$$

$$I_m^* = \frac{\mu E_m^*}{d_m+e_m}, S_M^* = \frac{b_M N_M + r_M R_M^*}{\beta_{mM} I_m^* + d_M}, E_M^* = \frac{\beta_{mM} S_M^* I_m^*}{(d_M+\eta)}$$

$$I_M^* = \frac{\eta E_H^*}{(d_e+\xi+d_M)} \text{ and } R_M^* = \frac{\xi I_M^*}{(r_M+d_M)}.$$

3.1 Basic reproduction number:

We are using the next generation operator approach as described by Diekmann, Heestebeek, and Metz in [47] to define the reproductive number, R_0, as the number of secondary infections that one infectious individual would create over the duration of the infectious period, provided that everyone else is susceptible. It can be obtained by calculating *V* and *F*, where *V* is the rate of transfer of individuals inside and outside of the infectious compartment and *F* be the rate of new infection in compartment. Hence, by the equations we obtain,

$$V = \begin{bmatrix} d+e+\gamma & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\gamma & d+e+d_H+\alpha-\theta & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\alpha & r_H+d+e & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & d_m+e_m+\mu & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu & d_m+e_m & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \eta+d_M & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\eta & d_M+d_e+\xi & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\xi & d_M+r_M \end{bmatrix}$$

$$\text{and } F = \begin{bmatrix} 0 & 0 & 0 & 0 & \beta_{mH} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_{Hm} & \beta_{Hm} & 0 & 0 & 0 & \beta_{Mm} & \beta_{Mm} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_{mM} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

The basic reproduction number is defined as the dominant Eigenvalue of FV^{-1} that is,

$$R_0 = \sqrt{\frac{\mu[\eta\xi\beta_{mM}\beta_{Mm}(d+e+d_H+\alpha-\theta)(d+e+\gamma)(r_H+d+e-d_M-r_M)+\gamma\beta_{mH}\beta_{Hm}(d_M+d_e+\xi)(d_M+r_M)(\eta+d_M)(r_H+d+e+\alpha)]}{(d_M+d_e+\xi)(d_M+r_M)(d_m+e_m)(d+e+d_H+\alpha-\theta)(d_m+e_m+\mu)(\eta+d_M)(d+e+\gamma)(r_H+d+e)}}$$

Theorem 3.1 *The disease-free equilibrium point is locally asymptotically stable if $R_0<1$ and unstable if $R_0>1$.*
Proof: See Appendix 3.

4. Numerical Simulation & its analysis:

In this section, we present the results of our numerical simulations. While the parasite transmission efficacy between vector and human hosts is well established for true human malarias, data for knowlesi parasite transmission are lacking. Using some classic parameter values that have been recorded for human malarias from real life observations [48,49,50] and some parameters are assumed for simulation as shown in Table 3.

Table 3

Parameter	Symbol	Value
Recruitment rate of humans	b_H	0.4417
Recruitment rate of mosquito	b_m	0.4227
Recruitment rate of monkeys	b_M	0.423
Natural death rate of humans	d	0.04212
Natural death rate of mosquito	d_m	0.8279
Immigration rate of humans.	e	0.3217
Immigration rate of mosquito	e_m	0.12
Transmission probability for malaria in human	β_{mH}	0.008333
Transmission probability for malaria by infected & recovered human	β_{Hm}	0.008
Transmission probability for malaria in monkey	β_{mM}	0.009333
Transmission probability for malaria by infected & recovered monkey in mosquito population	β_{Mm}	0.08
Transmission rate from Exposed to Infected class for Human	γ	0.8333
Transmission rate from infected to recovered class for Human	α	0.8704
Transmission rate from Exposed to Infected class for Monkey	η	0.45
Transmission rate from infected to recovered class for Monkey	ξ	0.065
Death rate by malaria in Human	d_H	0.0004493
Death rate by malaria in Monkey	d_e	0.000889
Transmission rate from recovered class to susceptible in Human	r_H	0.09704
Transmission rate from exposed to infected mosquito	μ	0.1
Vertical transmission	θ	0.0001
Transmission rate from recovered class to susceptible in Human	r_M	0.0098
Death rate by malaria in Human	d_M	0.3

Runge-Kutta method of order 4 is used to solve and MATLAB is used to simulate the model using above parametric values with following initial conditions:
Total Population of humans, mosquitoes & monkeys are N_h=10,000, N_m=3,000 and N_M=1,000 respectively.
Initial susceptible, exposed, infected and recovered population for humans are $S_h(0)$=10,000, $E_h(0)$=0, I_h=0 and $R_h(0)$=0 respectively. Similarly, for monkey population $S_M(0)$=900, $E_M(0)$=100, I_M=0 and $R_M(0)$=0. Initial susceptible population of mosquito, $S_m(0)$=2,900 and initial exposed & infected population of mosquito are $E_m(0)$=100, $I_m(0)$=0 respectively.
In figures 2,3 & 4, we compared the all classes of humans, mosquitoes & monkeys population with respect to time in months and in this cases the basic reproduction number R_0 = 0.0038 during the comparison of all classes in three populations (Humans, Mosquitoes & Monkeys). Simulation results shows that the recovered class (R_H) of human population is much higher in comparison to the recovered class (R_M) of monkey population (figure 2 & 4) due to lack of medicines in monkey populations.

In figure 5, shows the effect of inoculation on the infected human population by taking different values of α, the transmission probability from infected to recovered class in human population. Holding treatment rate 10%, the inoculation from α=0.009704 to α=0.09704, the infected humans population dropped from 6,000 to less than 5,000. Consequently, when α=0.9704, the infected humans population reduced to less than 2,000. Thus, when the value of α increases, the number infected classes of human population decreases. In this case, the basic reproduction number is Ro= 0.0038 remains same for all values of α.

In figure 6,7 & 8 shows that the effect of sensitivity analysis due to different values of transmission probability for malaria in humans, mosquitoes and monkeys population respectively. The infected classes in human population for different values of the transmission probability for malaria β_{mH} =0.008333, β_{mH} =0.08333 and β_{mH} =0.8333 and its corresponding basic reproduction numbers Ro=0.0038, Ro=0.0113 and Ro=0.0354 respectively are shown in figure 6. The infected classes in mosquito population for different values of the transmission probability by infected & recovered monkey for malaria β_{Mm} =0.008, β_{Mm} =0.08 and β_{Mm} =0.8 and its corresponding basic reproduction numbers Ro=0.0036, Ro=0.0038 and Ro=0.0059 respectively are shown in figure 7. The infected classes in monkey population for different values of the transmission probability for malaria β_{mM} =0.009333, β_{mM} =0.09333 and β_{mM} =0.9333 and its corresponding basic reproduction numbers Ro=0.0038, Ro=0.0059 and Ro=0.0152 respectively are shown in figure 8. Thus, we concluded from figure 6,7 & 8 that when the value of tranmission probability for malaria increased, then the infected classes of all three population (Human, Mosquito & Monkey) and its corresponding values of basic reproduction number also increased.

In figure 9, shows the effect of inoculation on the infected monkey population by taking different values of ξ, the transmission probability from infected to recovered class in monkey population. Holding treatment rate 10%, the inoculation from ξ=0.0065 to ξ=0.065, the infected monkeys population dropped from 3,50 to less than 3,00. Consequently, when ξ=0.65, the infected humans population reduced to less than 2,50. Thus, when the value of ξ increases, the number infected classes of monkey population decreases and its corresponding basic reproduction number increases. For the different values of ξ=0.0065, ξ=0.065 and ξ =0.65, its corresponding reproduction numbers are Ro= 0.0036, Ro=0.0038 and Ro=0.0051 respectively as shown in figure 9.

Figure 10 shows that when Ro > 1, the model is unstable. It is clear from figure 10 that when Ro= 1.018 > 1, the number of infected human population increases rapidly from zero to more than 12,000 in short time interval. So, the epidemic model of malaria is unstable when Ro>1.

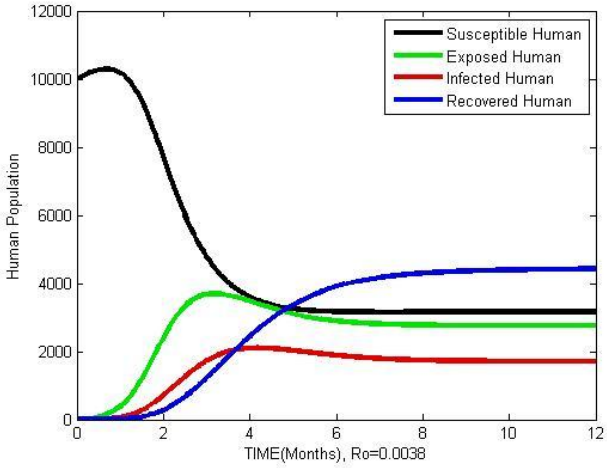

Figure 2: Human population when R_0 = 0.0038

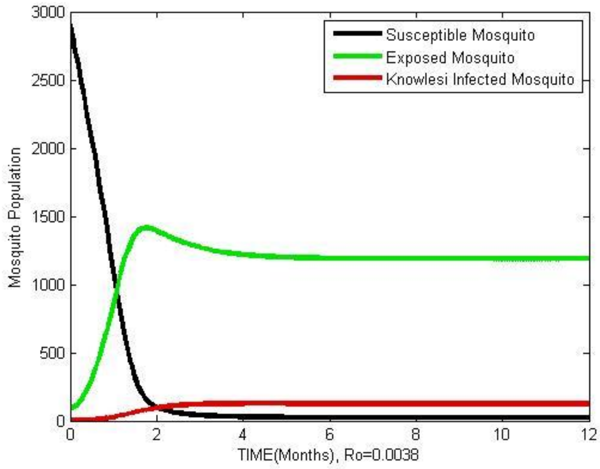

Figure 3: Mosquito population when R_0 = 0.0038

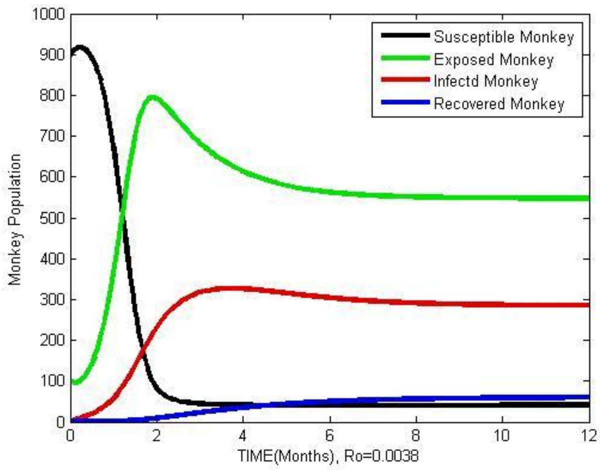

Figure 4: Monkey population when R_0 = 0.0038

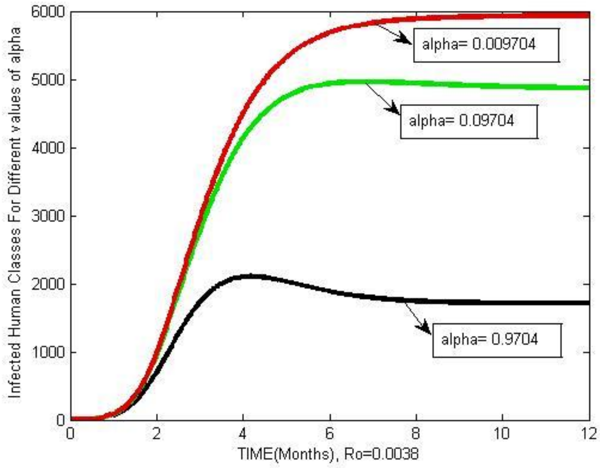

Figure 5: Infected Classes in Human population for different values of α (alpha)

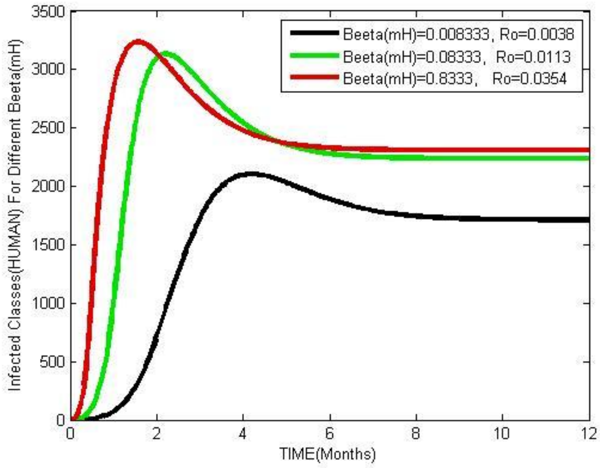

Figure 6: Infected Classes in Human Population for different values of β_{mH}

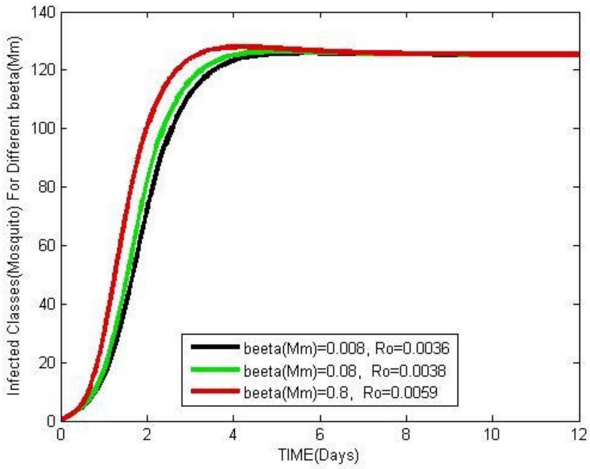

Figure 7 : Infected Classes in Mosquito Population for different values of β_{Mm}

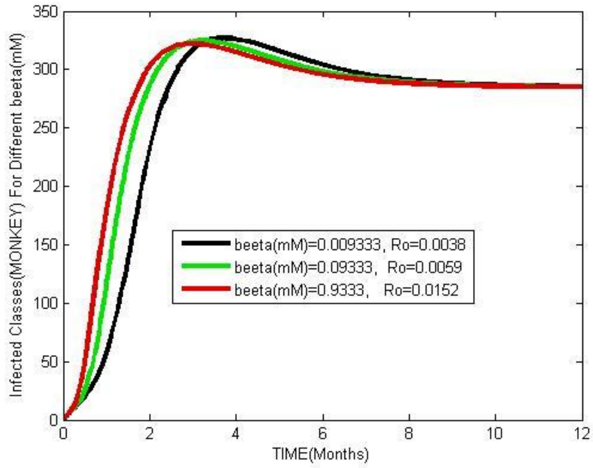

Figure 8: Infected Classes in Monkey Population for different values of β_{mM}

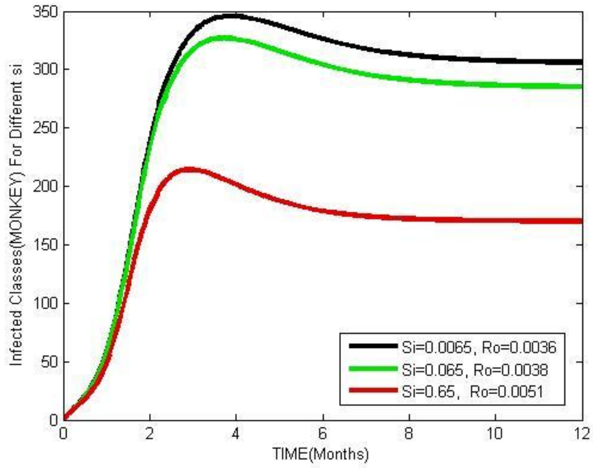

Figure 9: Infected Classes in Monkey Population for different values of ξ (Si)

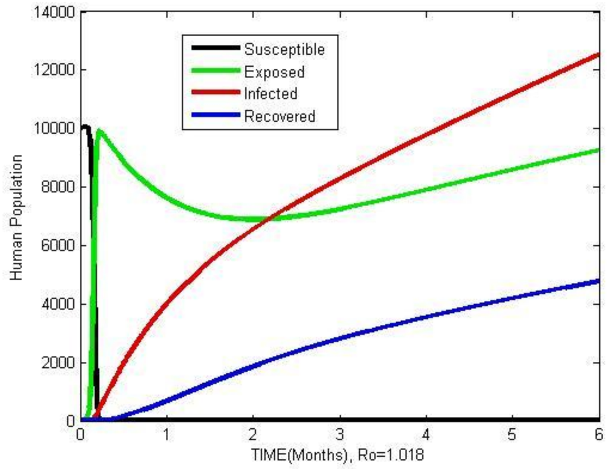

Figure 10 : Human Population when Ro > 1.

5. Conclusion:

We have developed a mathematical model of malaria for plasmodium knowlesi by taking three population of humans, mosquitoes and monkey. We formulated $S_HE_HI_HR_H$ model for human population, $S_mE_mI_m$ model for mosquito population and $S_ME_MI_MR_M$ model for monkey population. We find basic reproduction number Ro and prove that the disease-free equilibrium is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. Numerical simulation are presented to illustrate the results. From the simulations with realistic parameter sets, the endemic steady states is possible for our malaria model and it is stable when $R_0 = 0.0038< 1$ (Figure 2) and unstable when $R_0 =1.018 > 1$ (figure 10). From figure 2 and figure 4, it is clear that the recovered class (R_H) of human population is much higher in comparison to the recovered class (R_M) of monkey population due to lack of medicines in monkey populations. In figure 5, shows the effect of inoculation on the infected human population by taking different values of α, the transmission probability from infected to recovered class in human population. Holding treatment rate 10%, the inoculation from α=0.009704 to α=0.09704, the infected humans population dropped from 6,000 to less than 5,000. Consequently, when α=0.9704, the infected humans population reduced to less than 2,000. Thus, when the value of α increases, the number infected classes of human population decreases. In figure 6,7 & 8 shows that the effect of sensitivity analysis due to different values of transmission probability for malaria in humans, mosquitoes and monkeys population respectively and we concluded from it that when the value of tranmission probability for malaria increased, then the infected classes of all three population (Human, Mosquito & Monkey) and its corresponding values of basic reproduction number also increased. In figure 9, shows the effect of inoculation on the infected monkey population by taking different values of ξ, the transmission probability from infected to recovered class in monkey population. Holding treatment rate 10%, the inoculation from ξ=0.0065 to ξ=0.065, the infected monkeys population dropped from 3,50 to less than 3,00. Consequently, when ξ=0.65, the infected humans population reduced to less than 2,50. Thus, when the value of ξ increases, the number infected classes of monkey population decreases and its corresponding basic reproduction number increases. For the different values of ξ=0.0065, ξ=0.065 and ξ =0.65, its corresponding reproduction numbers are Ro= 0.0036, Ro=0.0038 and Ro=0.0051 respectively. On the basis of our analysis, we conclude that if a vaccine or a simple preventive action were available, we must research the specific host type to target the control in order to eliminate the malaria. In area where we cannot target a control towards either child or adult host types to control malaria, our model shows that, we can always target a control to mosquitoes to eliminate the malaria. It is a well known result. But elimination of mosquitoes does not appear to be feasible in an endemic area where the density of mosquitoes is very large in case of plasmodium knowlesi, because it exists mostly in three population areas (human, mosquito & monkey). Even if these measures are feasible it is very difficult and costly.

Finally, there are so many mathematical models on malaria has been developed till now as we have discussed in section 2, but our model is the only mathematical model on malaria due to plasmodium knowlesi parasite in three population (human, mosquito & monkey) with extensive numerical simulations and sensitivity analysis of basic reproduction number. It is also possible to validate our model by applying it to smaller population, and then to a larger population. This will allow us to make informed decisions about the level of intervention strategies, which provide the most effective way of minimizing the incidence of malaria.

In future, we may extend this model by considering quarantined and vaccination class in human population.

References

(1) Knowles, R., Das Gupta, B. M., 1932, A study of monkey-malaria and its experimental transmission to man, Indian Med. Gaz., 67, pp. 301-320.

(2) Chin, W., Contacos, P. G., Coatney, G. R., Kimball, HR, 1965,A naturally acquired quotidian-type malaria in man transferable to monkey, Science, 149, pp. 865.

(3) Yap, L. F., Cadigan, F. C., Coatney, G. R., 1971, A presumptive case of naturally occurring Plasmodium knowlesi malaria in man in Malaysia, Trans. Royal Soc. Trop. Med. Hyg., 65, pp. 839-840.

(4) Singh, B., Lee, K. S., Matusop, A., Radhakrishnan, A., 2004, A large focus of naturally acquired Plasmodium knowlesi infections in human beings, Lancet, 363**,** pp. 1017-1024.

(5) Jongwutiwes, S., Putaporntip, C., Iwasaki, T., Sata, T., Kanbara, H., 2004, Naturally acquired Plasmodium knowlesi malaria in human, Thailand, Emerg. Infect Dis., 10, pp. 2211-2213.

(6) Zhu, H. M., Li, J., Zheng, H., 2006, Human natural infection of Plasmodium knowlesi, Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi, 24, pp. 70-71 (in Chinese).

(7) Cox-Singh, J., Singh, B., 2008, Knowlesi malaria: newly emergent and of public health importance?, Trends Parasitol., 24, pp. 406-410.

(8) Luchavez, J., Espino, F., Curameng, P., Espina, R., 2008, Human infections with Plasmodium knowlesi, the Philippines, Emerg. Infect Dis., 14, pp. 811-813.

(9) Ng, O.T., Ooi, E.E., Lee, C.C., Jarrod, L.P., 2008, Naturally acquired human Plasmodium knowlesi infection, Singapore, Emerg. Infect Dis., 14, pp. 814-816.

(10) Kantele, A., Marti H., Felger, I., Muller D., Jokiranta T.S., 2008, Monkey malaria in a European traveler returning from Malaysia, Emerg. Infect Dis., 14, pp. 1434-1436.

(11) Bronner, U.P., Divis, P.C., Fa¨ rnert, A., Singh, B., 2009, Swedish traveler with Plasmodium knowlesi malaria after visiting Malaysian Borneo, Malar. J., 8**,** pp. 15.

(12) Vythilingam I., NoorAzian Y.M., Tan C.H., Jiram A.I., 2008, Plasmodium knowlesi in humans, macaques and mosquitoes in peninsular Malaysia, Parasit. Vectors, 1, pp. 26.

(13) Chin, W., Contacos, P.G., Collins, W.E., Jeter, M.H., Alpert, E., 1968, Experimental mosquito-transmission of Plasmodium knowlesi to man and monkey, Am. J. Trop. Med. Hyg., 17, pp. 355-358.
(14) Wharton, R.H., Eyles, D.E., 1961, Anopheles hackeri, a vector of Plasmodium knowlesi in Malaysia, Science, 134, pp. 279-280.
(15) Vythilingam, I., Tan, C.H., Asmad, M., Chan, S.T., Lee, K.S., Singh B., 2006, Natural transmission of Plasmodium knowlesi to humans by Anopheles latens in Sarawak, Malaysia, Trans. R. Soc. Trop. Med. Hyg., 100, pp. 1087-1088.
(16) Vythilingam, I., 2010, Plasmodium knowlesi in humans: a review on the role of its vectors in Malaysia, Trop. Biomed., 27, pp. 1-12.
(17) Tan, C.H., Vythilingam, I., Matusop, A., Chan, S.T., Singh, B., 2008, Bionomics of Anopheles latens in Kapit, Sarawak, Malaysian Borneo in relation to the transmission of zoonotic simian malaria parasite Plasmodium knowlesi. Malar. J.,7, pp. 52.
(18) Sallum, M.A.M., Peyton E.L., Harrison B.A., Wilkerson R.C., 2005, Revision of the Leucosphyrus group of Anopheles, Rev. Bras. Entom., 49, pp. 1-152.
(19) Eyles, D.E., Laing, A.B.G., Dobrovolny, C.G., 1962, The malaria parasites of the pigtailed macacque, Macaca nemestrina (Linnaeus) in Malaya, Indian J. Malariol., 16, pp. 285-298.
(20) Garnham P.C.C., 1966, Malaria Parasites and Other Haemosporidia. Blackwell Scientific Publications.
(21) Anderios F., NoorRain A., Vythilingam I., 2010, In vivo study of human Plasmodium knowlesi in Macaca fascicularis, Experimental Parasitology, 124, pp. 181-189.
(22) Eyles, D.E., Laing, A.B.G., Warren, M., Sandoshan, A.A., 1962, Malaria parasites of the malayan leaf monkeys of the genus Presbytis. Med. J. Malaysia, 17, pp. 85-86.
(23) Antinori, S., Galimberti, L., Milazzo, L., Corbellino, M., 2013, Plasmodium knowlesi: The emerging zoonotic malaria parasite, Acta Tropica, 125, pp. 191-201.
(24) Coatney, G.R., Collins, W.E.,Warren M., Contacos P.G., 1971, Plasmodium knowlesi: In The Primate Malaria, US Government Printing Office, Washington, DC, pp. 317-331.
(25) Napier, I.E., Campbell, H.G.M., 1932, Observations on a Plasmodium infection which causes haemoglobinuria in certain species of monkey, Indian Medical Gazette, 67, pp. 151-160.
(26) Fooden, J., 2006, Comparative review of fascicularis-group species of macaques (Primates: Macaca). Fieldiana Zoology, 107, pp. 1-43.
(27) Lee, K.S., Divis, P.C., Zakaria, S.K., Matusop, A., Julin, R.A., Conway, D.J., 2011, Plasmodium knowlesi: reservoir hosts and tracking the emergence in humans and macaques, Plos Pathogens, 7, pp. e1002015.
(28) Jongwutiwes, S., Buppan, P., Kosuvin, R., Seethmachai, S., Pattanawong, U., Sirichaisinthop, J.,. 2011, Plasmodium knowlesi malaria in humans and macaques, Thailand, Emerg. Infect. Dis., 17, pp. 1799-1806.
(29) Daneshvar, C., Davis, T.M., Cox-Singh, J., 2009, Clinical and laboratory features of human *Plasmodium knowlesi* infection, Clin. Infect. Dis., 49, pp. 852-860.
(30) Bruneel, F., Hocqueloux L., Alberti C., Wolff M., Chevret S., Bédos J.P., 2003, The clinical spectrum of severe imported falciparum malaria in the intensive care unit, Report of 188 cases in adults, Am. J. Respir. Crit. Care Med.,167, pp. 684-689.
(31) Schwake, L., Steit, J.P., Edler, L., Encke, J., Stremmel, W., Junghanss, T., 2008, Early treatment of imported falciparum malaria in the intensive care unit setting: an 8-year single-center retrospective study, Critical Care, 12, pp. R22.
(32) Cox-Singh J., Hiu J., Lucas S.B., Divis P.C., Zulkarnaen M., Chandran P., 2010, Severe malaria—a case of fatal Plasmodium knowlesi infection with post-mortem findings: a case report, Malar. J., 9, pp. 10.
(33) Fatih, F.A., Siner, A., Ahmed, A., Woon, L.C., Craig, A.G., Singh, B., 2012, Cytoadherence and virulence-the case of Plasmodium knowlesi malaria. Malar. J., 11, pp. 33.
(34) Cox-Singh J., Davis T.M., Lee K.S., Shamsul S.S., Matusop A., Ratnam S., 2008, Plasmodium knowlesi malaria in humans is widely distributed and potentially life threatening, Clin. Infect. Dis., 46, pp. 165-171.
(35) William, T., Menon, J., Rajahram, G., Chan L., Ma G., Donaldson S., 2011, Severe Plasmodium knowlesi malaria in a tertiary care hospital, Sabah, Malaysia, Emerg. Infect. Dis., 17, pp. 1248-1255.
(36) Macdonald. G., 1957, The Epidemiology and Control of Malaria, Oxford University Press, London,.
(37) Dietz K., Molineaux L., Thomas A., 1974, A malaria model tested in the African savannah, Bull. World Health Organ., 50, pp. 347-357.
(38) Aron J. L., 1988, Mathematical modeling of immunity to malaria, Math. Biosci., 90, pp. 385-396.
(39) Bailey N.J.T., 1975, The Mathematical Theory of Infectious Diseases and Its Application, Griffin, London.
(40) Anderson R. M., May R. M., 1991, Infectious Diseases of Humans: Dynamics and Control, Oxford University Press, Oxford, UK.
(41) Aron, J. L., May, R. M., 1982, The population dynamics of malaria, in The Population Dynamics of Infectious Disease: Theory and Applications, R. M. Anderson, ed., Chapman and Hall, London, pp. 139-179.
(42) Nedelman, J., 1985, Introductory review: Some new thoughts about some old malaria models, Math. Biosci., 73, pp. 159-182.
(43) Irwin, D. E., Cordon-Rosales C., Padilla N., 2002, Dynamic malaria models with environmental changes, in Proceedings of the Thirty-Fourth

Southeastern Symposium on System Theory, Huntsville, AL pp. 396-400.
(44) Yang, H. M., 2000, Malaria transmission model for different levels of acquired immunity and temperature-dependent parameters (vector), Rev. Sa´ude P´ublica, 34, pp. 223-231.
(45) Bacaer, N., Sokhna, C., 2005, A reaction-diffusion system modeling the spread of resistance to an antimalarial drug, Math. Biosci. Engrg., 2, pp. 227-238.
(46) Koella, J. C., Boete, C., 2003, A model for the co-evolution of immunity and immune evasion in vector-borne disease with implications for the epidemiology of malaria, Am. Nat., 161, pp. 698-707.
(47) Diekmann, O., Heesterbeek, J.A.P., Metz, J.A.J., 1990, On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations, J. Math. Biol., 28, pp. 365-382.
(48) Chitnis, N., Cushing, J. M., Hyman, J. M., 2006, Bifurcation Analysis of a Mathematical Model for Malaria Transmission, SIAM J. APPL. MATH., 67, pp. 24-45.
(49) Lawi, G.O., Mugisha, J.Y.T., Omolo-Ongati, N., 2011, Mathematical Model for Malaria and Meningitis Co-infection among Children, Appl. Math. Sci., 5, pp. 2337-2359.
(50) Pongsumpun, P., Tang, I.M., 2009, Mathematical model of Plasmodium Vivax and Plasmodium Falciparum Malaria, International Journal of Mathematical Models and Methods in applied sciences, 3.
(51) Esteva, L., Vargas, C., 1998, Analysis of a dengue disease transmission model, Math. Biosci., 150, pp. 131-151.
(52) Marsden, J.E., McCracken, M., 1976, The Hopf Bifurcation and its application, Springer-Verlag, New York.

Appendix 1

Symptoms and clinical findings in patients at Kapit Hospital with knowlesi and other malarias [28]

Data shown as %, median (interquartile range) or mean±standard deviation.

Symptoms	Knowlesi (n=107)	Falciparum (n=24)	Vivax (n=21)
Fever/Chills	100	92	95
Headache	94.4	87.5	52.4
Rigors	89.7	79.2	85.7
Malaise	89.7	91.7	66.7
Anorexia	83.2	70.8	52.4
Myalgia	97.9	79.2	90.2
Cough	56.1	54.7	47.6
Nausea	56.1	87.5	28.5
Abdominal pain	52.3	37.5	23.8
Vomiting	33.6	41.7	19
Diarrhoea	29	47.5	33.3
Clinical finding			
Axillary temperature(^{o}C)	37.6 (37.0-38.5)	37.8 (37.0 -38.5)	37.0 (36.8)
Respiratory rate (beats per minute)	26 (22-31)	25.5 (22.3-29.5)	27 (24.5-29.0)
Pulse rate (beats/min)	95±16	99±17	97±18
Arterial blood pressure (mm Hg)	89±11	85±9	89±9
Capillary refill time (secs)	2 (2-3)	2 (2-3)	2 (2-3)
Palpable liver	24.3	29.2	16.7
Palpable spleen	15	20.8	23.8

Appendix 2

Summary of WHO criterion reported in cases of severe P. knowlesi malaria in comparison with severe imported P. falciparum malaria [29,30,31,32,33,34].

	P. knowlesi N = 46 (%)	P. falciparum N = 310 (%)
Male/ Female	28/18	207/103
Age, median years	56(38-84)	38
Severe malaria (%)	46/1341 (3.4)	127/310 (40.9)
Platelets/µL, median(range)	34.000 (3000-130.000)	18.000-34.000
Cerebral malaria (unrousable coma)	0	37/310 (11.9)
Convulsions	0	2/310 (0.6)
Jaundice/hyperbilirubinemia	21/43 (48.8)	68/310 (21.9)
Acute renal failure	24/46 (52.2)	52/310 (16.8)
Hypoglicemia	6/40 (15)	6/310 (1.9)
DIC/bleeding	0	26/310 (8.4)

Shock/hypotension	22/46 (47.8)	25/310 (8.1)
Lactic acidosis	12/43 (27.9)	23/310 (7.4)
Respiratory distress	30/46 (65.2)	14/310 (4.5)
Severe anaemia	0	8/310 (2.6)
Hyperparasitaemia	21/46 (45.6)	52/210 (24.8)
More than one WHO criterion in the same patient	36/46 (78.3)	44/210 (20.9)
Death	19/1341 (1.4)	10/310 (3.2)

Appendix 3

The jacobian matrix of our model at disease-free condition is as follows:

$$\begin{bmatrix} -d-e & 0 & 0 & r_H & 0 & 0 & -\beta_{mH} & 0 & 0 & 0 & 0 \\ 0 & -d-e-\gamma & 0 & 0 & 0 & 0 & \beta_{mH} & 0 & 0 & 0 & 0 \\ 0 & \gamma & -d-e-d_H-\alpha+\theta & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \alpha & -r-d-e & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\beta_{Hm} & -\beta_{Hm} & -d_m-e_m & 0 & 0 & 0 & 0 & -\beta_{Mm} & -\beta_{Mm} \\ 0 & 0 & \beta_{Hm} & \beta_{Hm} & 0 & -d_m-e_m-\mu & 0 & 0 & 0 & \beta_{Mm} & \beta_{Mm} \\ 0 & 0 & 0 & 0 & 0 & \mu & -d_m-e_m & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\beta_{mM} & -d_M & 0 & 0 & r_M \\ 0 & 0 & 0 & 0 & 0 & 0 & \beta_{mM} & 0 & -\eta-d_M & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \eta & -d_M-d_e-\xi & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \xi & -d_M-r_M \end{bmatrix}.$$

The characteristic equation of the Jacobian is given by:

λ^8+(-M-K-G-D-Y-I-W-U)λ^7+(DK+IK+KW+KM+KY+KU+GK+GM+YU+GW+MU+ UW+ IM+DM+DG+YW+IY+MY+DI+GY+DU+DW+IW+MW+GU+GI+DY+IU)λ^6+(-GUW-GMY-GMW-DYW-DGM-KDI-MKY-DMU-KGI-KIW-KIU-KIY-KIM-DGK-DUW-DMY-DMW-DYU-DGY-DGW-GYU-GYW-DKU-GMU-MYU-MYW-GIU-GIW-IMU-IMW-IYW-IMY-DGI-DIY-DIM-DIU-IUW-IYU-GKM-KYW-MUW-YUW-DIW-GIY-MKU-DGU-KYU-DKY-GIM-GKU-DKW-KUW-GKW-GKY-DKM-MKW)λ^5+(GKYU-FJNC+DGKW+KYUW+ GMKW+GMKY+DKUW+DGKM+DMKW+DMKY+DGKY+KMYW+DKYW+KMYU+GKYW+DGKU+DKYU+KMUW+DMKU+GKUW+DGMY+GMKU+KGIW+KDIY+KDGI+KIYW+KIUW+KIMW+KDIM+KGIU+KIMU+KIYU+KIMY+KGIY+KDIU+KGIM+GYUW+KDIW+DGYU+MYUW+DGUW+DGIU+DGMW+GMUW+DGMU+GMYU+GMYW+DGYW+DMYW+DMUW+DMYU-NPTL+IMUW+IYUW+IMYW+DYUW+IMYU+DIYW+ DIUW+ DIMW+DIYU+DGIY+DGIW+GIYU+GIMU+GIMY+DIMY+DIMU+DGIM+GIYW+GIUW+GIMW) λ^4 + (-KGIMW-KGIYW-DGMYW-DGYUW-GMYUW-DGMYU+GNPTL-KDGIU-KDIMY-KDIYU-KDIMU-DIMYW-DIYUW-DIMUW-DIMYU-KMYUW+DNPTL-DMYUW-DGMUW+NPTLW-NPTLV-KGIUW-KDGIW-KDGIY-KGIYU-GKYUW-GKMUW-DGMKU-KGIMU-KDGIM-KGIMY-KIMYW-KIMYU+FJNCY-KIYUW-KIMUW-IMYUW-DGIYU-DGIUW+FJNCW-DGIMU-DGIMW-GIMUW-GIYUW+FJNCU-DGKYU-GIMYU-DGMKW-GIMYW-GKMYU-DGIYW-KDIUW-GKMYW-DKMYW-DGIMY-DGMKY-DGKYW-KDIMW-KDIYW-DKMYU-DGKUW-DKYUW+INPTL-FHJNC-DKMUW+ FJNCI)λ^3 + (GNPTLV+DGMYUW+KDGIYW-GNPTLW+KDGIMY+GKMYUW-FJNCIW-FJNCIU-FJNCIY+FHJNCY+DIMYUW-DNPTLW+DNPTLV-DGNPTL+KGIMUW+ KGIMYU+ KGIMYW+KDGIYU+DGKYUW-FJNCYW+KDGIMU+DGKMUW-DINPTL-FJNCUW+KIMYUW-FJNCYU+DGIMYU+DGKMYW+KDIMUW+KDIMYU+KDIMYW+ KDIYUW+GIMYUW-GINPTL+DGIMUW+DGKMYU+DGIYUW+DGIMYW+INPTLV-INPTLW+DKMYUW+FHJNCU+KDGIUW+FHJNCW+KGIYUW+KDGIMW)λ^2 + (-KDIMYUW-GINPTLV-FHJNCUW+DGNPTLW-DGIMYUW-DINPTLV-KGIMYUW-KDGIMUW+FJNCIUW-KDGMYUW-KDGIYUW-DGNPTLV-FHJNCYU-FHJNCYW+DINPTLW-KDGIMYU+DGINPTL+FJNCYUW+GINPTLW+FJNCIYW + FJNCIYU-KDGIMYW) λ-DGINPTLW+DGINPTLV-FJNCIYUW+KDGIMYUW+ FHJNCYUW).

Where A=-(d+e), B= r_H, C=-β_{mH}, D=-(d+e+γ), F= γ, G=(d+e+ d_H+α-θ), H= α, I=-(r+d+e), J=-β_{Hm}, K=-(d_m+e_m), L=-β_{Mm}, M=-(d_m+e_m+μ), N= μ, P=-β_{mM}, Q=-d_M, R= r_M, S=-(η+d_M), T= η, U=-(d_M+d_e+ξ), V=ξ, W=-(d_M+r_M), and Y= η-d_M.

To evaluate the signs of the roots of above characteristic equation, we first use the Routh-Hurwitz criteria to prove that when $R_0 < 1$, all roots of above characteristic equation have negative real part. Then, using Descates's rule of sign, we prove that when $R_0 > 1$, there is one positive real root.

Now to apply Routh-Hurwitz criteria [51,52], let $a_1 = (-M-K-G-D-Y-I-W-U)$, a_2 = DK+IK+KW+KM+KY+KU+GK+GM+YU+GW+MU+ UW+ IM+DM+DG+YW+IY+MY+DI+GY+DU+DW+IW+MW+GU+GI+DY+IU a_3 = (-GUW-GMY-GMW-DYW-DGM-KDI-MKY-DMU-KGI-KIW-KIU-KIY-KIM-DGK-DUW-DMY-DMW-DYU-DGY-DGW-GYU-GYW-DKU-GMU-MYU-MYW-GIU-GIW-IMU-IMW-IYW-IMY-DGI-DIY-DIM-DIU-IUW-IYU-GKM-KYW-MUW-YUW-DIW-GIY-MKU-DGU-KYU-DKY-GIM-GKU-DKW-KUW-GKW-GKY-DKM-MKW), a_4 = +(GKYU-FJNC+DGKW+KYUW+ GMKW+GMKY+DKUW+DGKM+DMKW+DMKY+DGKY+KMYW+DKYW+KMYU+GKYW+DGKU+DKYU+KMUW+DMKU+GKUW+DGMY+GMKU+KGIW+KDIY+KDGI+KIYW+KIUW+KIMW+KDIM+KGIU+KIMU+KIYU+KIMY+KGIY+KDIU+KGIM+GYUW+KDIW+DGYU+MYUW+DGUW+DGIU+DGMW+GMUW+DGMU+GMYU+GMYW+DGYW+DMYW+DMUW+DMYU-NPTL+IMUW+IYUW+IMYW+DYUW+IMYU+DIYW+ DIUW+ DIMW+DIYU+DGIY+DGIW+GIYU+GIMU+GIMY+DIMY+DIMU+DGIM+GIYW+GIUW+GIMW), a_5 = (-KGIMW-KGIYW-DGMYW-DGYUW-GMYUW-DGMYU+GNPTL-KDGIU-KDIMY-KDIYU-KDIMU-DIMYW-DIYUW-DIMUW-DIMYU-KMYUW+DNPTL-DMYUW-DGMUW+NPTLW-NPTLV-KGIUW-KDGIW-KDGIY-

KGIYU-GKYUW-GKMUW-DGMKU-KGIMU-KDGIM-KGIMY-KIMYW-KIMYU+FJNCY-KIYUW-KIMUW-IMYUW-DGIYU-DGIUW+FJNCW-DGIMU-DGIMW-GIMUW-GIYUW+FJNCU-DGKYU-GIMYU-DGMKW-GIMYW-GKMYU-DGIYW-KDIUW-GKMYW-DKMYW-DGIMY-DGMKY-DGKYW-KDIMW-KDIYW-DKMYU-DGKUW-DKYUW+INPTL-FHJNC-DKMUW+ FJNCI)

$$a_6 = (\mathrm{GNPTLV} + \mathrm{DGMYUW} + \mathrm{KDGIYW} - \mathrm{GNPTLW} + \mathrm{KDGIMY} + \mathrm{GKMYUW} - \mathrm{FJNCIW} - \mathrm{FJNCIU} - \mathrm{FJNCIY} + \mathrm{FHJNCY} + \mathrm{DIMYUW} - \mathrm{DNPTLW} + \mathrm{DNPTLV} - \mathrm{DGNPTL} + \mathrm{KGIMUW} + \mathrm{KGIMYU} + \mathrm{KGIMYW} + \mathrm{KDGIYU} + \mathrm{DGKYUW} - \mathrm{FJNCYW} + \mathrm{KDGIMU} + \mathrm{DGKMUW} - \mathrm{DINPTL} - \mathrm{FJNCUW} + \mathrm{KIMYUW} - \mathrm{FJNCYU} + \mathrm{DGIMYU} + \mathrm{DGKMYW} + \mathrm{KDIMUW} + \mathrm{KDIMYU} + \mathrm{KDIMYW} + \mathrm{KDIYUW} + \mathrm{GIMYUW} - \mathrm{GINPTL} + \mathrm{DGIMUW} + \mathrm{DGKMYU} + \mathrm{DGIYUW} + \mathrm{DGIMYW} + \mathrm{INPTLV} - \mathrm{INPTLW} + \mathrm{DKMYUW} + \mathrm{FHJNCU} + \mathrm{KDGIUW} + \mathrm{FHJNCW} + \mathrm{KGIYUW} + \mathrm{KDGIMW})$$

$$a_7 = (-\mathrm{KDIMYUW} - \mathrm{GINPTLV} - \mathrm{FHJNCUW} + \mathrm{DGNPTLW} - \mathrm{DGIMYUW} - \mathrm{DINPTLV} - \mathrm{KGIMYUW} - \mathrm{KDGIMUW} + \mathrm{FJNCIUW} - \mathrm{KDGMYUW} - \mathrm{KDGIYUW} - \mathrm{DGNPTLV} - \mathrm{FHJNCYU} - \mathrm{FHJNCYW} + \mathrm{DINPTLW} - \mathrm{KDGIMYU} + \mathrm{DGINPTL} + \mathrm{FJNCYUW} + \mathrm{GINPTLW} + \mathrm{FJNCIYW} + \mathrm{FJNCIYU} - \mathrm{KDGIMYW})$$

and $a_8 = \mathrm{DGINPTLW} + \mathrm{DGINPTLV} - \mathrm{FJNCIYUW} + \mathrm{KDGIMYUW} + \mathrm{FHJNCYUW}$.

The Hurwitz matrices of above characteristic equation are as follows:

$$H_1 = [a_1],\ H_2 = \begin{bmatrix} a_1 & 1 \\ a_3 & a_4 \end{bmatrix},\ H_3 = \begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{bmatrix},\ H_4 = \begin{bmatrix} a_1 & 1 & 0 & 0 \\ a_3 & a_2 & a_1 & 1 \\ a_5 & a_4 & a_3 & a_2 \\ a_7 & a_6 & a_5 & a_4 \end{bmatrix},$$

$$H_5 = \begin{bmatrix} a_1 & 1 & 0 & 0 & 0 \\ a_3 & a_2 & a_1 & 1 & 0 \\ a_5 & a_4 & a_3 & a_2 & a_1 \\ a_7 & a_6 & a_5 & a_4 & a_3 \\ 0 & a_8 & a_7 & a_6 & a_5 \end{bmatrix},\ H_6 = \begin{bmatrix} a_1 & 1 & 0 & 0 & 0 & 0 \\ a_3 & a_2 & a_1 & 1 & 0 & 0 \\ a_5 & a_4 & a_3 & a_2 & a_1 & 1 \\ a_7 & a_6 & a_5 & a_4 & a_3 & a_2 \\ 0 & a_8 & a_7 & a_6 & a_5 & a_4 \\ 0 & 0 & 0 & a_8 & a_7 & a_6 \end{bmatrix},$$

$$H_7 = \begin{bmatrix} a_1 & 1 & 0 & 0 & 0 & 0 & 0 \\ a_3 & a_2 & a_1 & 1 & 0 & 0 & 0 \\ a_5 & a_4 & a_3 & a_2 & a_1 & 1 & 0 \\ a_7 & a_6 & a_5 & a_4 & a_3 & a_2 & a_1 \\ 0 & a_8 & a_7 & a_6 & a_5 & a_4 & a_3 \\ 0 & 0 & 0 & a_8 & a_7 & a_6 & a_5 \\ 0 & 0 & 0 & 0 & 0 & a_8 & a_7 \end{bmatrix},\ H_8 = \begin{bmatrix} a_1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ a_3 & a_2 & a_1 & 1 & 0 & 0 & 0 & 0 \\ a_5 & a_4 & a_3 & a_2 & a_1 & 1 & 0 & 0 \\ a_7 & a_6 & a_5 & a_4 & a_3 & a_2 & a_1 & 1 \\ 0 & a_8 & a_7 & a_6 & a_5 & a_4 & a_3 & a_2 \\ 0 & 0 & 0 & a_8 & a_7 & a_6 & a_5 & a_4 \\ 0 & 0 & 0 & 0 & 0 & a_8 & a_7 & a_6 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_8 \end{bmatrix}.$$

The determinant value of H_1 and H_2 are a_1 and $a_1a_4 - a_3$, both are positive, it is easily verified by putting the values of $a_1, a_3,$ and a_4. Similarly, the determinant values of H_3, H_4, H_5, H_6, H_7 and H_8 are $a_1a_2a_3 - a_1^2a_4 - a_3^2 + a_5a_1$, $a_1a_2a_3a_4 - a_1a_2^2a_5 - a_1^2a_4^2 + 2a_1a_4a_5 + a_6a_1^2a_2 - a_1a_6a_3 - a_3^2a_4 + a_3a_2a_5 - a_5^2 - a_7a_1a_2 + a_7a_3$,

$$a_4a_1^2a_6a_3 - a_1^2a_8a_3a_2 - a_1a_3^2a_2a_6 + a_1a_3a_7a_2^2 - a_1^2a_4^2a_5 + 2a_6a_7a_1^2 + a_8a_1^3a_4 - a_8a_5a_1^2 + a_1a_8a_3^2 - a_7a_3^2a_2 + a_6a_3^3 - a_5^3 - a_1^3a_6^2 + a_1a_2a_3a_4a_5 - a_1a_2^2a_5^2 + 2a_1a_4a_5^2 - a_3^2a_4a_5 + a_3a_2a_5^2 + 2a_7a_3a_5 - a_7^2a_1 + 2a_2a_5a_1^2a_6 - a_2a_7a_1^2a_4 - 3a_1a_6a_3a_5 - a_7a_1a_2a_5,$$

$$-3a_1a_3a_6^2a_5 - 3a_1a_3a_8a_7a_2 - 2a_3a_7^2a_4 - a_1a_3a_8a_2^2a_5 + a_3^2a_4^2a_7 + 3a_3a_6a_7a_5 + a_1a_3a_7a_6a_4 - a_1a_3^2a_6^2a_2 - 2a_8a_1^2a_5a_6 + 2a_8a_1a_7a_5 - a_1^2a_4^2a_3a_8 - a_5a_1a_6a_2a_7 - 3a_6a_7a_1^2a_4a_2 - a_7^2a_1a_2^3 + a_7a_3^2a_8 + 2a_4a_5a_1a_3a_8 + a_1a_3a_4a_6a_2a_5 - a_3^2a_4a_6a_5 + 2a_1a_3a_6a_2^2a_7 - 2a_3^2a_6a_7a_2 + a_1a_3^2a_8a_4a_2 + a_3^2a_8a_2a_5 + 3a_7^2a_1a_4a_2 + a_7a_1a_4a_2^2a_5 - a_7a_4a_2a_3a_5 - a_7^2a_5a_2 + 2a_5a_1^2a_6^2a_2 - a_5^2a_1a_2^2a_6 + a_5^2a_2a_6a_3 - a_1a_3a_4^2a_7a_2 + a_1a_3^2a_8a_6 + a_3^3a_6^2 - a_3^3a_8a_4 - a_5^3a_6 - a_8a_5^2a_3 + 3a_6^2a_7a_1^2 - 3a_6a_7^2a_1 + 2a_8a_1^2a_2^2a_7 + a_1^2a_4^3a_7 + a_7^3 - a_1^3a_6^3 - a_8^2a_1^3a_2 + a_5^2a_7a_4 + a_8^2a_1^2a_3 + 2a_8a_1^3a_6a_4 - 2a_8a_1^2a_7a_4 - a_1^2a_4^2a_5a_6 - 2a_1a_4^2a_5a_7 + 2a_5^2a_1a_6a_4 - a_8a_1^2a_2a_6a_3 + a_1^2a_6^2a_4a_3 + a_7^2a_3a_2^2,$$

$$a_7^2a_4a_5^2 + 3a_7^3a_1a_4a_2 + a_8^3a_1^4 + a_7a_1^2a_4a_8a_2a_5 - 3a_7^2a_1^2a_4a_6a_2 + 3a_1^2a_3a_8^2a_2a_5 + a_1a_3a_7^2a_6a_4 + a_1a_3^2a_8a_6a_2a_5 + 2a_1a_3a_6a_2^2a_7^2 - 4a_1a_3^2a_8^2a_5 - a_1^2a_3a_8a_6a_2a_7 - a_3^3a_8a_6a_5 + a_1a_3^2a_8a_6a_7 + 3a_3^2a_8a_7a_5a_2 - 3a_1a_3a_8a_2^2a_5a_7 + 2a_7a_1a_4a_5^2a_6 + 4a_7a_1a_4a_8a_3a_5 - a_7^2a_4a_5a_3a_2 + a_7^2a_1a_4a_2^2a_5 - a_7a_5^3a_6 - a_7^3a_5a_2 + a_7a_5^2a_8a_1a_2 + a_7a_5^2a_6a_2a_3 - a_7^2a_5a_6a_1a_2 - a_5^2a_1a_2^2a_6a_7 - 5a_8a_5a_1^2a_6a_7 - 2a_5a_1a_7^2a_4^2 + 2a_5a_1^2a_6^2a_2a_7 - 2a_8a_5^2a_1^2a_6a_2 + a_7^3a_2^2a_3 + a_3^3a_6^2a_7 - 2a_3^2a_6a_7^2a_2 - 3a_1a_3a_5a_6^2a_7 + 3a_3a_7^2a_5a_6 - 4a_3a_8a_7a_5^2 - 5a_1a_3a_8a_7^2a_2 - 2a_3a_7^3a_4 + 2a_3^2a_8a_7^2 - a_1a_3^3a_8^2a_2 - 3a_7^2a_1^2a_4a_8 - a_8^2a_1^3a_6a_3 + a_8^2a_1^2a_3^2a_4 - 2a_8^2a_1^3a_4a_5 + 3a_8a_1^2a_2^2a_7^2 - a_7^3a_1a_2^3 + 4a_1^2a_3a_8^2a_7 - a_8a_5^3a_2a_3 + a_3^2a_8a_4a_5^2 - a_3^2a_4a_5a_6a_7 - a_1a_3a_4^2a_7^2a_2 + a_3^2a_4^2a_7^2 + 2a_1a_3^2a_8a_4a_7a_2 - 2a_3^3a_8a_4a_7 - a_1a_3^2a_6^2a_7a_2 - a_8a_1^2a_6a_4a_3a_5 + 3a_8a_1^3a_6a_4a_7 - a_1^2a_4^2a_5a_6a_7 - 2a_8a_1^2a_4^2a_7a_3 + a_1^2a_6^2a_7a_4a_3 + 3a_1a_3a_8a_5^2a_6 + a_1a_3a_4a_2a_5a_6a_7 - a_1a_3a_8a_4a_2a_5^2 + a_3^4a_8^2 + 2a_8^2a_5^2a_1^2 + a_8a_5^4 + a_7^4 + 4a_7^2a_5a_8a_1 + a_1^2a_4^3a_7^2 - a_1^3a_6^3a_7 + a_8a_1^3a_6^2a_5 + a_8a_5^3a_1a_2^2 - 2a_8a_5^3a_1a_4 - 3a_6a_7^3a_1 + 3a_6^2a_7^2a_1^2 - 3a_8^2a_1^3a_2a_7 + a_8a_1^2a_4^2a_5^2,$$

$$
\begin{aligned}
a_8(a_7^2a_4a_5^2 + 3a_7^3a_1a_4a_2 + a_8^3a_1^4 + a_7a_1^2a_4a_8a_2a_5 \\
& - 3a_7^2a_1^2a_4a_6a_2 + 3a_1^2a_3a_8^2a_2a_5 \\
& + a_1a_3a_7^2a_6a_4 + a_1a_3^2a_8a_6a_2a_5 \\
& + 2a_1a_3a_6a_2^2a_7^2 - 4a_1a_3^2a_8^2a_5 \\
& - a_1^2a_3a_8a_6a_2a_7 - a_3^3a_8a_6a_5 \\
& + a_1a_3^2a_8a_6a_7 + 3a_3^2a_8a_7a_5a_2 \\
& - 3a_1a_3a_8a_2^2a_5a_7 + 2a_7a_1a_4a_5^2a_6 \\
& + 4a_7a_1a_4a_8a_3a_5 - a_7^2a_4a_5a_3a_2 \\
& + a_7^2a_1a_4a_2^2a_5 - a_7a_5^3a_6 - a_7^3a_5a_2 \\
& + a_7a_5^2a_8a_1a_2 + a_7a_5^2a_6a_2a_3 \\
& - a_7^2a_5a_6a_1a_2 - a_5^2a_1a_2^2a_6a_7 \\
& - 5a_8a_5a_1^2a_6a_7 - 2a_5a_1a_7^2a_4^2 \\
& + 2a_5a_1^2a_6^2a_2a_7 - 2a_8a_5^2a_1^2a_6a_2 + a_7^3a_2^2a_3 \\
& + a_3^3a_6^2a_7 - 2a_3^2a_6a_7^2a_2 - 3a_1a_3a_5a_6^2a_7 \\
& + 3a_3a_7^2a_5a_6 - 4a_3a_8a_7a_5^2 \\
& - 5a_1a_3a_8a_7^2a_2 - 2a_3a_7^3a_4 + 2a_3^2a_8a_7^2 \\
& - a_1a_3^3a_8^2a_2 - 3a_7^2a_1^2a_4a_8 - a_8^2a_1^3a_6a_3 \\
& + a_8^2a_1^2a_3^2a_4 - 2a_8^2a_1^3a_4a_5 + 3a_8a_1^2a_2^2a_7^2 \\
& - a_7^3a_1a_2^3 + 4a_1^2a_3a_8^2a_7 - a_8a_5^3a_2a_3 \\
& + a_3^2a_8a_4a_5^2 - a_3^2a_4a_5a_6a_7 - a_1a_3a_4^2a_7^2a_2 \\
& + a_3^2a_4^2a_7^2 + 2a_1a_3^2a_8a_4a_7a_2 - 2a_3^3a_8a_4a_7 \\
& - a_1a_3^2a_6^2a_7a_2 - a_8a_1^2a_6a_4a_3a_5 \\
& + 3a_8a_1^3a_6a_4a_7 - a_1^2a_4^2a_5a_6a_7 \\
& - 2a_8a_1^2a_4^2a_7a_3 + a_1^2a_6^2a_7a_4a_3 \\
& + 3a_1a_3a_8a_5^2a_6 + a_1a_3a_4a_2a_5a_6a_7 \\
& - a_1a_3a_8a_4a_2a_5^2 + a_3^4a_8^2 + 2a_8^2a_5^2a_1^2 \\
& + a_8a_5^4 + a_7^4 + 4a_7^2a_5a_8a_1 + a_1^2a_4^3a_7^2 \\
& - a_1^3a_6^3a_7 + a_8a_1^3a_6^2a_5 + a_8a_5^3a_1a_2^2 \\
& - 2a_8a_5^3a_1a_4 - 3a_6a_7^3a_1 + 3a_6^2a_7^2a_1^2 \\
& - 3a_8^2a_1^3a_2a_7 + a_8a_1^2a_4^2a_5^2)
\end{aligned}
$$

respectively. By putting the values of $a_1, a_2, a_3, a_4, a_5 , a_6, a_7, a_8$, we get the determinant values of H_3, H_4, H_5, H_6, H_7 and H_8 are also positive.

When $R_0 < 1$, all the coefficients, a_i, of the characteristic equation and H_1, H_2, H_3, H_4 H_5, H_6, H_7 and H_8, are positive, so by the Routh-Hurwitz criteria, all the eigenvalues of the Jacobian have negative or negative real part, and the disease-free equilibrium point is stable.

When $R_0 > 1$, there is one and only one sign change in the sequence $a_1, a_2, a_3, \ldots, a_8$, so by Descartes's rule of sign there is one eigenvalue with positive real part, and the disease-free equilibrium point is unstable.

Thus, the disease-free equilibrium point is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.■