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Dengue fever: Mathematical modelling and computer simulation

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Abstract

Dengue fever is a re-emergent disease affecting people in more than 100 countries. Its incidence has increased fourfold since 1970 and nearly half the world's population is now at risk. In the present paper, a mathematical model is proposed to simulate the succession of two epidemics with variable human populations. Stability analysis of the equilibrium points is carried out and a simulation is given for different parameter settings.

Keywords: Dengue fever; Dengue haemorrhagic fever; Vaccination program mathematical model; Stability analysis; Simulation

1. Introduction

Infectious diseases were the main causes of death during the last millennium. Life expectancy was often limited by recurrent uncontrolled epidemics. After the second World War, with medical research achievements in terms of vaccination, antibiotics and improvement of life conditions, it was expected that infectious diseases were going to disappear. Consequently, in developed countries, the efforts have been concentrated on Non-Communicable Diseases (NCDs) such as Cardio Vascular Diseases (CVDs) and cancer. However, at the dawn of the third millennium, the world population is facing a double burden of NCDs and infectious diseases. NCDs, once known as the disease of "the rich", are now sweeping the entire globe with the main part of the increasing trend attributable to developing countries where CVDs, cancer and diabetes are flourishing [1–5]. The socio-economic transition engaged by medium income countries is believed to be responsible for this evolution. But, at the same time, infectious diseases continue to be the major causes of mortality and morbidity in developing countries. Well known existing, emerging and reemerging diseases like tuberculosis, cholera, meningitis, hepatitis, malaria, dengue, yellow fever, AIDS, Ebola, SARS and others are causing suffering and mortality to a wide population in the developing world, but those in developed countries are also at risk [6,7]. Measured in terms of numbers of deaths and Disability Adjusted Life Years (DALYs) (which is a combination of Years Lived with Disability (YLD) and Years of Life Lost from premature death (YLL)) [8], the

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burden of these diseases is alarming and calls for urgent action and efficient strategies. If the present trend is maintained, developing countries, with poor budgets and ill-health systems, will not be able to cope with the double burden of infective and non-infective diseases. Among the infectious diseases, dengue fever, especially known in Southeast Asia, is now endemic in more than 100 countries worldwide. Its incidence has increased fourfold since 1970 and nearly half the world's population (2.5–3 billion) is now at risk. In 1998, 1.2 million cases were reported to WHO in 56 countries. It is estimated that more than 50 million people are infected every year of which half a million are affected by DHF [9]. The two recognised species of the vector transmitting dengue are Aedes aegypti and Aedes albopictus. The former is highly anthropophilic, thriving in crowded cities and biting primarily during the day while the latter is less anthropophilic and inhabits rural areas. Consequently, the importance of dengue is twofold: (i) With increasing urbanisation, crowded cities, poor sanitation and lack of hygiene, environmental conditions foster the spread of the disease which, even in the absence of fatal forms, breeds significant economic and social costs (absenteeism, immobilisation, debilitation, medication). (ii) The potential risk of evolution towards the haemorrhagic form and the shock syndrome with high economic costs and which may lead to death. In the two cases, the burden of disease can be measured in terms of DALYs. Dengue fever clearly illustrates the links between health and sustainable development. Any tentative steps to predict the epidemics and prevent the disasters caused by the disease will impose a global strategy that takes into account environmental conditions, levels of poverty and illiteracy, and eventually, degree of coverage by vaccination programs.

For a better understanding of the disease dynamics, there is a need to diagnose all the parameters and their effects (geographic, economic, social, biologic). To this aim, data should be gathered, organised and analysed and consequent strategies can be formulated and again tested and evaluated. Weekly epidemiological record, Dengue bulletin and DengueNet constitute interesting tools but there is still a long way to go in order to overcome unreported and underestimated situations. Indeed, according to a prospective study conducted recently in north-east Brazil, the authors estimated that around 560 000 individuals were infected by one or two serotypes of dengue, whereas the official system of notification had recorded only 360 cases [10]. Concrete multivariable data will also allow for better development of mathematical models, computer software and biomedical issues.

The re-emergence of dengue and its wide spreading during the last few decades constitute a major problem for the World Health Organisation and health authorities in developing countries in particular. With more than 2.5 billion people at risk, the disease is necessitating a large effort for the comprehension of its dynamics, the evaluation of its impact and the search for means of control. Many authors have presented the disease as a major health problem either for the last decades of the 20th century or for the third millennium [11–14]. The need for research and surveillance is often dealt with and many authors have stressed that DF/DHF is still perceived as unimportant and receives little attention despite its social and economic impact being similar to some of the most visible infectious diseases [15–17]. Finally, among the dengue control strategies, vaccination is the most promising. So far, the difficulties in elaborating a vaccine stemmed from the fact that the vaccine must protect against the four serotypes at the same time. Research is encouraged, supported by cost-effective analysis in order to produce a vaccine in the very short term. The Cost effectiveness of a pediatric dengue vaccine was discussed through a model of vaccinating children at 15 months in Southeast Asia. The economic feasibility of a pediatric tetravalent vaccine was ascertained by comparing the gross and net cost per 1000 population (of all ages) with the cost per DALY saved. According to the author's conclusion, the potential vaccine would be highly cost effective [18].

Different mathematical models were proposed. In general, they use compartmental dynamics with Susceptible, Exposed, Infective and Removed for human; and Susceptible and Infective for mosquito. SEIRS models were considered in [19] with an evaluation of the impact of ultra-low volume (ULV) insecticide applications on dengue epidemics. The values of basis parameters used in simulation by the authors constituted a data source (Table 1) for other authors. A general model with the population of susceptible and infectious humans assumed constant and facing only one virus was considered by Esteva and Varga [20]. The authors also proposed models where the human population was supposed to grow exponentially and to have a constant disease rate [21], two serotypes of virus and variable human population [22], and the impact of vertical transmission and interrupted feeding on the dynamics of the disease [23]. In [23], considering competitive

exclusion of one of the strains as a result of the interaction, the authors argue that the existence of this phenomenon is the product of the interaction between a superinfection process and frequency-dependent host contact rates. Assuming that dengue epidemics are strongly influenced by the amount of rainfall amongst other environmental factors, a model with varying vector population was considered in [24]. According to the Report of the Scientific Working Group on Insect and Human Health [25], the sequencing of the entire Aedes aegypti genome, anticipated to be completed by 2004, will open an unparalleled opportunity to explore the interaction of dengue viruses with the vector. The report indicates how modelling with bioinformatics will provide research with interesting tools. While pointing out that the idea of two viruses coexisting in the same epidemic is controversial, mathematical models with a constant human population (N_h) and two different viruses acting at separated intervals of time were considered by the authors in previous papers [26,27]. Building on that, the present paper deals with a variable human population ($N_h(t)$).

2. Formulation of the model and stability analysis

2.1. Parameters of the model

Let N_h and N_v denote the human and vector population sizes. In this model death is proportional to the population size with a rate constant μ_h and we assume a constant Λ_h due to births and immigrations. So $\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h$ whereas for vector population we suppose that N_v is constant.

The human population (respectively of mosquito population) of size N_h (resp. N_v) formed of Susceptibles S_h, of Infective I_h and of Removed R_h (resp. S_v and I_v).

The model supposes a homogeneous mixing of human and mosquito populations so that each bite has an equal probability of being taken from any particular human. While noting b_s the average biting rate of susceptible vectors, p_{hv} the average transmission probability of an infectious human to a susceptible vector, the rate of exposure for vectors is given by $(p_{hv} I_h b_s)/N_h$. It is admitted [20] that some infections increase the number of bites by the infected mosquitoes in relation to the susceptible; therefore, we will assume that the rate of infected mosquito bites b_i is greater than the one of the susceptible mosquitoes b_s.

Noting p_{vh} the average transmission probability of an infectious vector to human and I_v the infectious vector number, the rate of exposure for humans is given by $(p_{vh} I_v b_i)/N_h$ so:

- The adequate contact rate of humans to vectors is given by $C_{hv} = p_{hv} b_s$.
- The adequate contact rate of vectors to humans is given by $C_{vh} = p_{vh} b_i$.

The human life span is taken equal to 25 000 days (68.5 years), and the one of the vector is of 4 days. Other parameter values are given in Table 1 in the following section.

Table 1
Definitions and values of basis parameters used in simulations [19]

Name of the parameter	Notation	Base value
Transmission probability of vector to human	p_{hv}	0.75
Transmission probability of human to vector	p_{vh}	0.75
Bites per susceptible mosquito per day	b_s	0.5
Bites per infectious mosquito per day	b_i	1.0
Effective contact rate, human to vector	C_{hv}	0.375
Effective contact rate, vector to human	C_{vh}	0.75
Human life span	$\frac{1}{\mu_h}$	25 000 days
Vector life span	$\frac{1}{\mu_v}$	4 days
Host infection duration	$\frac{1}{\mu_h+\gamma_h}$	3 days

2.2. Basis parameters

2.3. Equations of the model

A schematic representation of the model is shown in Fig. 1.

We consider a compartmental model that is to say that every population is divided into classes, and that one individual of a population passes from one class to another with a suitable rate.

Up to now there is no vaccine against dengue viruses but research is going on and the eventuality of an immunization program is not excluded in the medium term. In this study we investigate the effect of such an immunization option and we also discuss the possibility of a partial vaccination against each serotype that will enable the control of the second epidemic and the evolution of dengue to dengue haemorrhagic fever.

In the case of the first epidemic, the simplest assumption is that a random fraction, **p**, of susceptible humans can permanently be immunized against all the four serotypes. While for the second epidemic, a partial immunization is applied to the one removed from the first epidemic. The dynamics of this disease in the host and vector populations is given by the following equations.

2.4. First epidemic

The model is governed by the following equations:

Human population

$$\begin{cases} \frac{dS_h}{dt} = \Lambda_h - (\mu_h + p + C_{vh} I_v / N_h) S_h, \\ \frac{dI_h}{dt} = (C_{vh} I_v / N_h) S_h - (\mu_h + \gamma_h + \alpha_h) I_h, \\ \frac{dR_h}{dt} = p S_h + \gamma_h I_h - \mu_h R_h, \\ \frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - \alpha_h I_h. \end{cases}$$

Vector population

$$\begin{cases} \frac{dS_v}{dt} = \mu_v N_v - (\mu_v + C_{hv} I_h / N_h) S_v, \\ \frac{dI_v}{dt} = (C_{hv} I_h / N_h) S_v - \mu_v I_v. \end{cases}$$

For this system the first orthant in the $S_h I_h R_h S_v I_v N_h$ space is positively invariant. Because $N_h'(t) < 0$ for $N_h > \Lambda_h/\mu_h$, all paths in the first orthant approach, enter or stay inside the subset Ω given by

$$\Omega = \{(S_h, I_h, S_v, I_v, N_h)/0 \leqslant S_v;\ 0 \leqslant I_v;\ 0 \leqslant I_h;\ 0 \leqslant S_h;\ S_h + I_h + R_h = N_h \leqslant \Lambda_h/\mu_h;\ S_v + I_v = N_v\}.$$

The continuity of the right side of the previous system and its derivatives implies that unique solutions exist in the maximal interval. Since solutions approach, enter or stay in Ω they are eventually bounded and hence exist for $t \geqslant 0$. Therefore the model is mathematically and epidemiologically well posed.

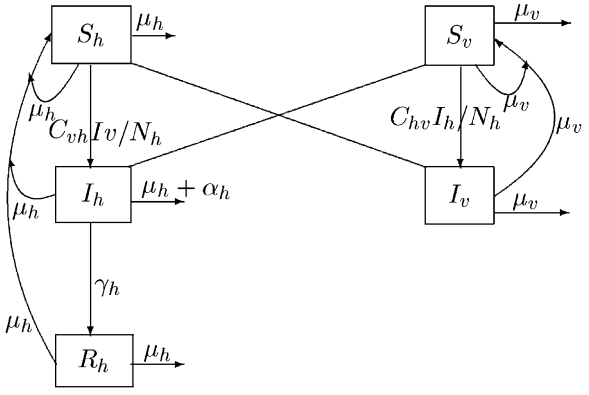

Fig. 1. Schematic diagram: compartments of human and vector populations.

Introducing the proportion

$$s_h = \frac{S_h}{\Lambda_h/\mu_h}, \quad i_h = \frac{I_h}{\Lambda_h/\mu_h}, \quad r_h = \frac{R_h}{\Lambda_h/\mu_h}, \quad s_v = \frac{S_v}{N_v}, \quad i_v = \frac{I_v}{N_v}$$

and with the conditions $S_h + I_h + R_h = N_h$ and $S_v + I_v = N_v$, so $R_h = N_h - S_h - I_h$ and $S_v = N_v - I_v$, the two previous systems become

$$\begin{cases} \frac{ds_h}{dt} = \mu_h - (\mu_h + p + C_{vh} m i_v/n_h) s_h, \\ \frac{di_h}{dt} = (C_{vh} m i_v/n_h) s_h - (\mu_h + \gamma_h + \alpha_h) i_h, \\ \frac{di_v}{dt} = C_{hv} i_h/n_h (1 - i_v) - \mu_v i_v, \\ \frac{dn_h}{dt} = \mu_h - \mu_h n_h - \alpha_h i_h \end{cases}$$

in the set $\Omega' = \{(s_h, i_h, i_v, n_h)/0 \leqslant i_h; 0 \leqslant s_h, s_h + i_h \leqslant n_h \leqslant 1; 0 \leqslant i_v \leqslant 1\}$ with $m = \frac{N_v}{\Lambda_h/\mu_h}$.

2.4.1. Equilibrium points

Theorem 1. *The previous system admits two equilibrium points*:

- *If* $\mu_h(R-1) \leqslant p$ *the trivial state* $E_1\left(\frac{\mu_h}{\mu_h+p}, 0, 0, 1\right)$ *is the only equilibrium.*
- *If* $\mu_h(R-1) > p$ *then an endemic equilibrium* $E_2(\overline{s_h}, \overline{i_h}, \overline{i_v}, \overline{n_h})$ *will also be in* Ω', *were* $R = \frac{mC_{hv}C_{vh}}{\mu_v(\mu_h+\gamma_h+\alpha_h)}$.

Proof. See Appendix A.1. □

2.4.2. Stability

Theorem 2

(i) *For* $R \leqslant \frac{\mu_h+p}{\mu_h}$ *the state* E_1 *is globally asymptotically stable* (*i.e.* $\lim_{t\to\infty} I_h(t) = 0$).
(ii) *For* $R > \frac{\mu_h+p}{\mu_h}$ *the state* E_2 *is locally asymptotically stable.*

Proof. See Appendix A.2. □

Remark 1

(i) The first point $E_1 = \left(\frac{\mu_h}{\mu_h+p}, 0, 0, 0\right)$ is trivial in the sense that all individuals are healthy and stay healthy all the time.
(ii) The second point is $E_2 = (s_h^*, i_h^*, i_v^*, n_h^*)$ which corresponds to the endemic state i.e. the case where the disease persists in the two populations.

Remark 2. The inequality $\mu_h(R-1) \leqslant p$ represents the principle of herd immunity because the susceptible population may be protected from epidemics if enough people are immunized.

2.5. Second epidemic

In the same way as in the previous section, we suppose the onset of a second epidemic with another virus. But in this case, we may assume that a proportion of the population of susceptibles is globally immunized against the four serotypes or partially immunized against one, two or three viruses.

But in this model we suppose that the human population is divided into two categories:

- A subpopulation that is infected once by serotype 2.
- A subpopulation SN_h that is infected twice: the first by serotype 1 and the second by serotype 2; this subpopulation is derived only from the removed from the first epidemic (serotype 1) who are exposed to DHF ($Sn_h(t_0) = Ss_h(t_0) = r_h^*$).

Therefore the model is given by the following equations:

Human population

$$\begin{cases} \frac{dS_h}{dt} = \Lambda_h - \mu_h S_h - \frac{C_{vh} I_v}{N_h} S_h - pS_h, \\ \frac{dI_h}{dt} = \frac{C_{vh} I_v}{N_h} S_h - (\mu_h + \gamma_h + \alpha_h) I_h, \\ \frac{dR_h}{dt} = \gamma_h I_h - \mu_h R_h + pS_h, \\ \frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - \alpha_h (I_h + SI_h), \\ \frac{dSS_h}{dt} = -\mu_h SS_h - \frac{C_{vh} I_N}{N_h} SS_h - pSS_h, \\ \frac{dSI_h}{dt} = \frac{C_{vh} I_v}{N_h} SS_h - (\mu_h + \gamma_h + \alpha_h) SI_h, \\ \frac{dSR_h}{dt} = \gamma_h SI_h - \mu_h SR_h + pSS_h. \end{cases}$$

Vector population

$$\begin{cases} \frac{dS_v}{dt} = \mu_v N_v - \frac{C_{vh}}{N_h} (I_h + SI_h) S_v - \mu_v S_v, \\ \frac{dI_v}{dt} = \frac{C_{vh}}{N_h} (I_h + SI_h)(N_v + I_v) - \mu_v I_v. \end{cases}$$

As in the first epidemic, introducing the proportion

$$s_h = \frac{S_h}{\Lambda_h/\mu_h}, \quad i_h = \frac{I_h}{\Lambda_h/\mu_h}, \quad r_h = \frac{R_h}{\Lambda_h/\mu_h}, \quad Ss_h = \frac{SS_h}{\Lambda_h/\mu_h}, \quad Si_h = \frac{SI_h}{\Lambda_h/\mu_h}, \quad Sr_h = \frac{SR_h}{\Lambda_h/\mu_h},$$
$$s_v = \frac{S_v}{N_v}, \quad i_v = \frac{I_v}{N_v}.$$

The previous two systems become

Human population

$$\begin{cases} \frac{ds_h}{dt} = \mu_h - \left(\mu + p + \frac{C_{vh} m i_v}{n_h}\right) s_h, \\ \frac{di_h}{dt} = \frac{C_{vh} i_v}{n_h} s_h - (\mu_h + \gamma_h + \alpha_h) i_h, \\ \frac{dr_h}{dt} = \gamma_h i_h - \mu_h r_h + p s_h, \\ \frac{dn_h}{dt} = \mu_h - \mu_h n_h - \alpha_h (i_h + Si_h), \\ \frac{dSs_h}{dt} = -\left(\mu_h + \frac{C_{vh} m i_v}{n_h} + p\right) Ss_h, \\ \frac{dSi_h}{dt} = \frac{C_{vh} i_v}{n_h} Ss_h - (\mu_h + \gamma_h + \alpha_h) Si_h, \\ \frac{dSr_h}{dt} = \gamma_h Si_h - \mu_h Sr_h + pSs_h. \end{cases}$$

Vector population

$$\begin{cases} \frac{dSs_v}{dt} = \mu_v - \frac{C_{hv}}{n_h} (i_h + Si_h) s_v - \mu_v s_v, \\ \frac{di_v}{dt} = \frac{C_{vh}}{n_h} (i_h + Si_h)(1 - i_v) - \mu_v i_v, \end{cases}$$

$Sn_h(t_0) = Ss_h(t_0) = r_h^*$ and with the conditions $s_h + i_h + r_h + Ss_h + Si_h + Sr_h = n_h$ and $s_v + i_v = 1$, so: $r_h = n_h - s_h - i_h - Sn_h$ and $s_v = 1_v - i_v$ were $\frac{dSn_h}{dt} = -\mu_h Sn_h - \alpha_h Si_h$ and $Sr_h = Sn_h - Ss_h - Si_h$ then

$$\begin{cases} \frac{ds_h}{dt} = \mu_h - \left(\mu + p + \frac{C_{vh} m i_v}{n_h}\right) s_h, \\ \frac{di_h}{dt} = \frac{C_{vh} i_v}{n_h} s_h - (\mu_h + \gamma_h + \alpha_h) i_h, \\ \frac{dr_h}{dt} = \gamma_h i_h - \mu_h r_h + p s_h, \\ \frac{dn_h}{dt} = \mu_h - \mu_h n_h - \alpha_h (i_h + S i_h), \\ \frac{di_v}{dt} = \frac{C_{vh}}{n_h} (i_h + S i_h)(1 - i_v) - \mu_v i_v, \\ \frac{dSs_h}{dt} = -\left(\mu_h + \frac{C_{vh} m i_v}{n_h} + p\right) S s_h, \\ \frac{dSi_h}{dt} = \frac{C_{vh} i_v}{n_h} S s_h - (\mu_h + \gamma_h + \alpha_h) S i_h, \\ \frac{dSn_h}{dt} = -\mu_h S n_h - \alpha_h S i_h. \end{cases}$$

Theorem 3. *The previous system admits two equilibrium points*:

- *If* $\mu_h(R-1) \leqslant p$ *the trivial state* $E_1\left(\frac{\mu_h}{\mu_h+p}, 0, 0, 1, 0, 0, 0\right)$ *is the only equilibrium.*
- *If* $\mu_h(R-1) > p$ *then an endemic equilibrium* $E_2(s_h^*, i_h^*, i_v^*, n_h^*, 0, 0, 0)$ *will also be in* Ω', *were* $R = \frac{m C_{hv} C_{vh}}{\mu_v(\mu_h+\gamma_h+\alpha_h)}$.

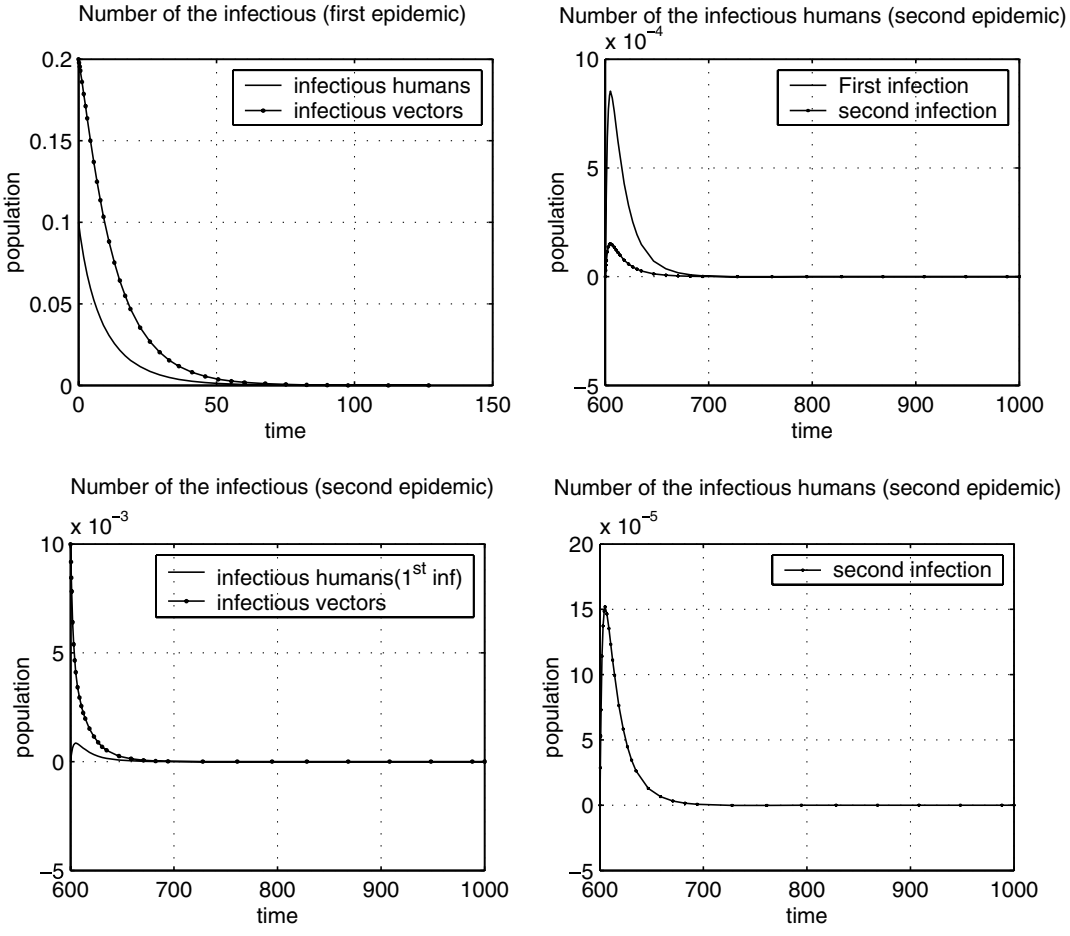

Fig. 2. Convergence ($R \leqslant 1$).

Proof. The equilibrium points satisfy the following relations:

$$\mu_h - \left(\mu + p + \frac{C_{vh} m i_v}{n_h}\right) s_h = 0, \tag{1}$$

$$\frac{C_{vh} i_v}{n_h} s_h - (\mu_h + \gamma_h + \alpha_h) i_h = 0, \tag{2}$$

$$\gamma_h i_h - \mu_h r_h + p s_h = 0, \tag{3}$$

$$\mu_h - \mu_h n_h - \alpha_h (i_h + S i_h) = 0, \tag{4}$$

$$\frac{C_{vh}}{n_h}(i_h + S i_h)(1 - i_v) - \mu_v i_v = 0, \tag{5}$$

$$-\left(\mu_h + \frac{C_{vh} m i_v}{n_h} + p\right) S s_h = 0, \tag{6}$$

$$\frac{C_{vh} i_v}{n_h} S s_h - (\mu_h + \gamma_h + \alpha_h) S i_h = 0, \tag{7}$$

$$-\mu_h S n_h - \alpha_h S i_h = 0. \tag{8}$$

From Eqs. (5)–(7) we have $Ss_h^* = 0, Si_h^* = 0$ and $Sn_h^* = 0$ and the proof follows as in Theorem 1.

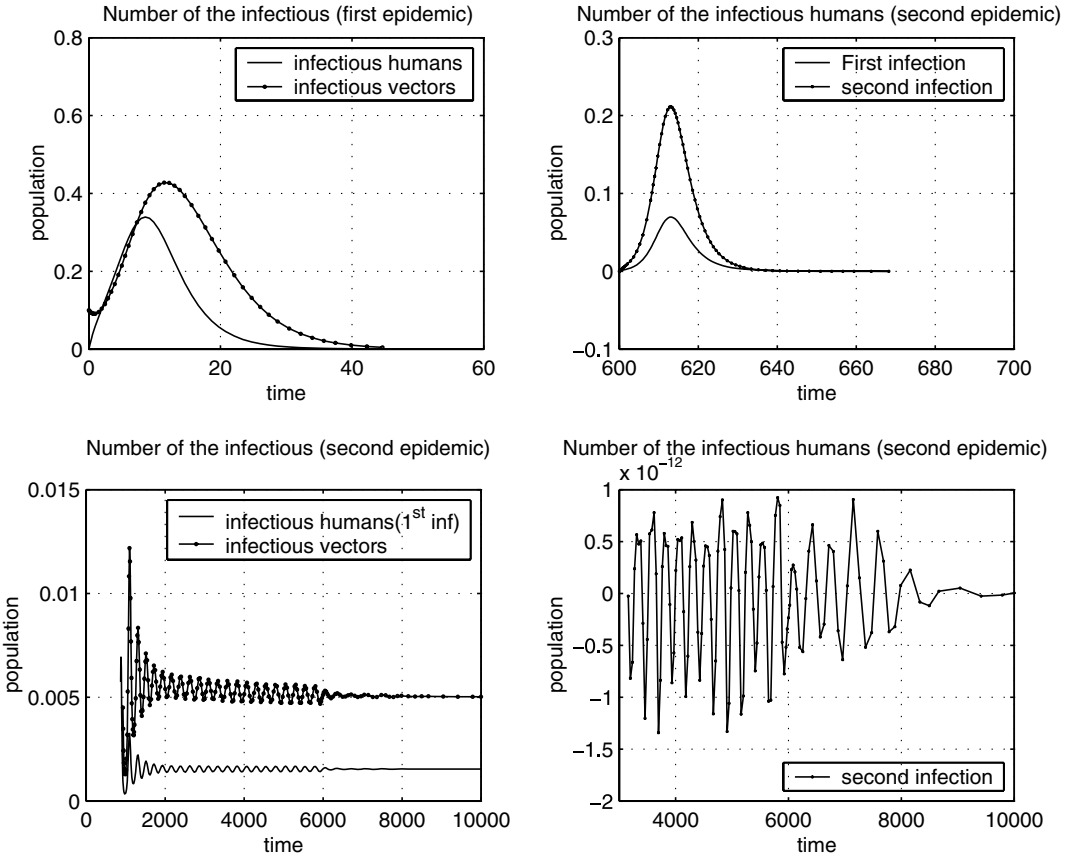

Fig. 3. Oscillation ($R > 1$).

2.5.1. Stability

Theorem 4

(i) *For* $R \leqslant \frac{\mu_h+r}{\mu_h}$ *the state* E_1 *is globally asymptotically stable* (*i.e.* $\lim_{t\to\infty} i_h(t) = 0$ *and* $\lim_{t\to\infty} Si_h(t) = 0$).
(ii) *For* $R > \frac{\mu_h+r}{\mu_h}$ *the state* E_2 *is locally asymptotically stable.*

Proof. See Appendix A.3. □

Remark 3. The inequality $\mu_h(R-1) \leqslant p$ represents the principle of herd immunity because the susceptible population may be protected from epidemics if enough people are immunized.

3. Results and discussion

Stability analysis was carried out for the two epidemics and values of the threshold were obtained. Illustration of the dynamics of each epidemic is given in Figs. 2–5.

Fig. 2 shows the typical behavior of the solutions indicating that the rate of susceptible, infectious and removed approaches, asymptotically, the trivial state of the system (the ideal state) i.e. to the case where all the population is and will remain healthy (in this case $R \leqslant 1$).

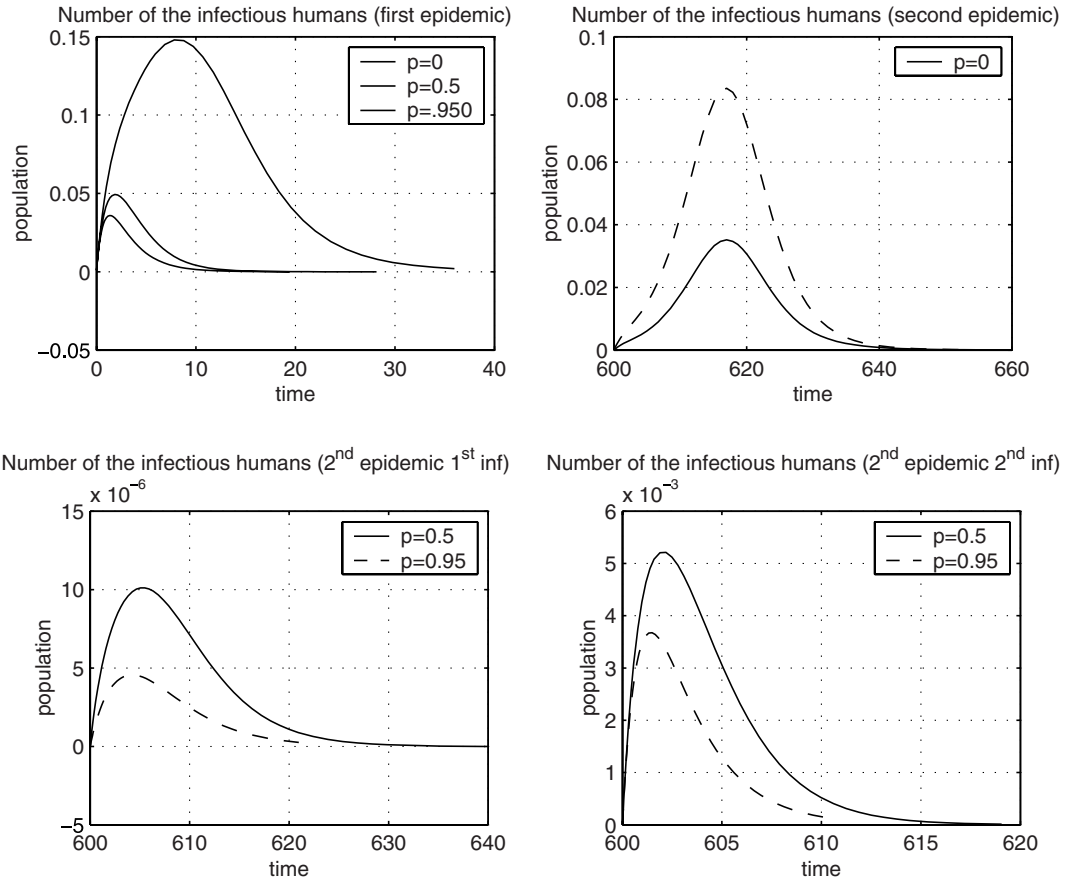

Fig. 4. The role of vaccination in the eradication of the disease in the first and second epidemics.

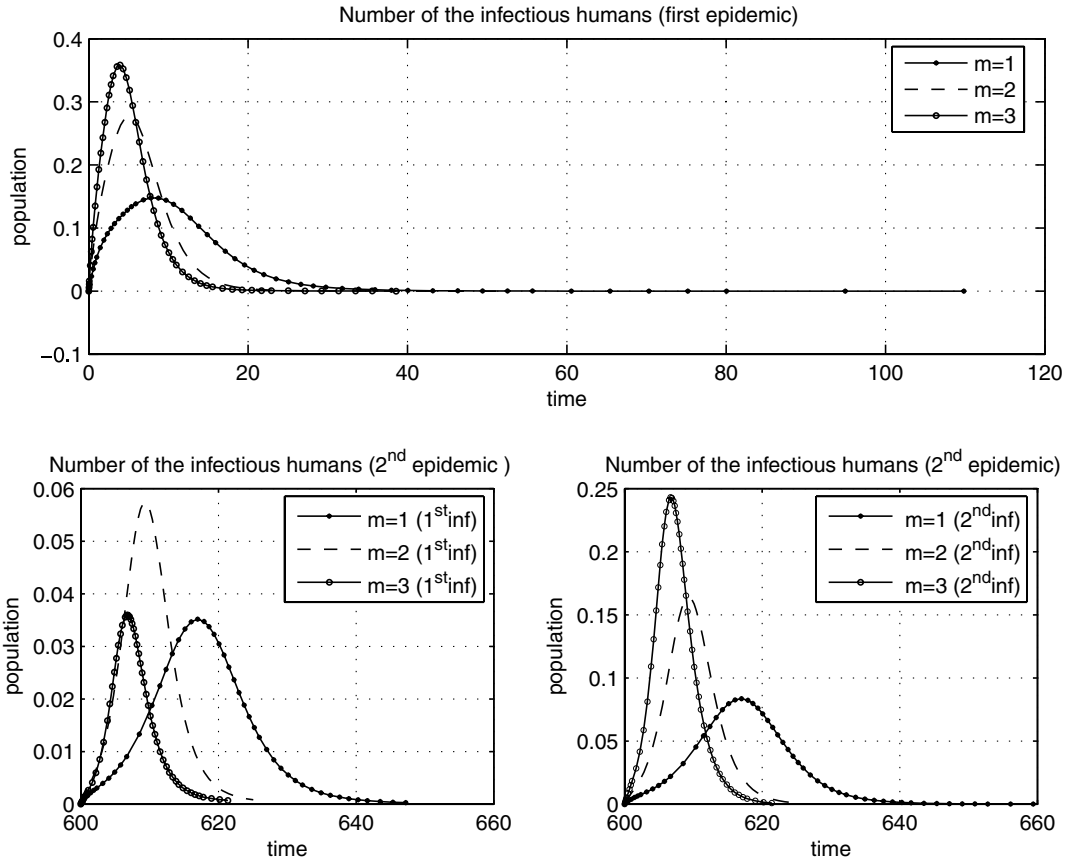

Fig. 5. The reduction of the population of vectors is not sufficient to eradicate dengue (model without vaccination (i.e. $p = 0$)).

Fig. 3 illustrates an oscillatory behavior near the neighborhood of the endemic equilibrium point. This behavior can be justified by the fact that if $R > 1$ and if the initial values of s_h, Ss_h and Ss_v satisfy the relation: $R(s_h + Ss_h + s_v) > 1$ then $(s_h + Ss_h + s_v)$ decreases and the rate of the infectious $(i_h + Si_h + i_v)$ grows until a maximum, then it decreases since there are not enough susceptible people to be infected. However after a low value of $(i_h + Si_h + i_v)$, the rate of susceptibles starts growing because of birth of new susceptibles, once the threshold is reached, an epidemic releases again and so forth.

Fig. 4 illustrates the benefits of vaccination in the control of the epidemic, a comparison is given for different values of the proportion ($p = 0$, 0.5 and 0.95), but this eventuality remains subject to the advent of the vaccine.

Fig. 5 gives a comparison between curves of the infectious of the first and the second infections for different values of $m = \frac{N_v}{\Lambda_h/\mu_h}$ and consequently implies values of the vector population N_v.

4. Conclusion

By nature, dengue is a complex disease resulting from the interaction of human, biological, environmental, geographical and socio-economic factors. The present paper is devoted to the understanding of the dynamics of dengue and essentially its evolution to the haemorrhagic form. The model considers a variable human population and the succession of two epidemics at different intervals of time. The reproductive number R as a threshold of control of the epidemics is discussed through stability analysis. Simulations with different parameter settings give an illustration of the succession of two epidemics and their amplitudes. The model shows that environmental management alone as a means of vector control is not sufficient; it can only delay the outbreak of the epidemics (Fig. 5). The eventuality of a vaccine protecting simultaneously against the four

serotypes remains a hope for the future. Meanwhile, partial vaccination could be part of a preventive strategy based on the control of environmental and socio-economic factors.

Appendix A

A.1. Proof of Theorem 1

The equilibrium points satisfy the following relations:

$$\mu_h - (\mu_h + p + mC_{vh}i_v/n_h)s_h = 0, \tag{9}$$

$$\frac{mC_{vh}i_v}{n_h}s_h - (\mu_h + \gamma_h + \alpha_h)i_h = 0, \tag{10}$$

$$\frac{C_{hv}i_h}{n_h}(1 - i_v) - \mu_v i_v = 0, \tag{11}$$

$$\mu_h - \mu_h n_h - \alpha_h i_h = 0. \tag{12}$$

From Eq. (11) we have

$$C_{hv}i_h/n_h(1 - i_v) - \mu_v i_v = 0$$
$$\Rightarrow \frac{C_{hv}i_h}{n_h} - \left(\frac{C_{hv}i_h}{n_h} + \mu_v\right)i_v = 0 \quad \text{thus } i_v = \frac{C_{hv}i_h}{C_{hv}i_h + \mu_v n_h}.$$

From Eq. (12) we have $n_h = \frac{\mu_h - \alpha_h i_h}{\mu_h}$ so

$$i_v = \frac{\mu_h C_{hv}i_h}{\mu_h C_{hv}i_h + \mu_v(\mu_h - \alpha_h i_h)} = \frac{\mu_h C_{hv}i_h}{(C_{hv}\mu_h - \alpha_h\mu_v)i_h + \mu_v\mu_h}.$$

From Eq. (9) we have

$$\mu_h - (\mu_h + p)s_h - \frac{C_{vh}}{n_h}i_v s_h = 0$$
$$\Rightarrow (\mu_h + p)s_h = \mu_h - \frac{C_{vh}}{n_h}i_v s_h.$$

On the other hand,

$$\frac{C_{vh}}{n_h}i_v s_h = (\mu_h + \gamma_h + \alpha_h)i_h \quad \text{then } s_h = \frac{\mu_h - (\mu_h + \gamma_h + \alpha_h)i_h}{\mu_h + p}.$$

From Eq. (10) we have $\frac{C_{vh}}{n_h}i_v s_h - (\mu_h + \gamma_h + \alpha_h)i_h = 0$ so

$$C_{vh}m\frac{\mu_h}{\mu_h - \alpha_h i_h}\frac{\mu_h C_{hv}i_h}{(C_{hv}\mu_h - \alpha_h\mu_v)i_h + \mu_h\mu_v}\frac{\mu_h - (\mu_h + \gamma_h + \alpha_h)i_h}{\mu_h + p} - (\mu_h + \gamma_h + \alpha_h)i_h = 0,$$

$$(C_{vh}m\mu_h^2 C_{hv}i_h)(\mu_h - (\mu_h + \gamma_h + \alpha_h)i_h) - (\mu_h + p)(\mu_h - \alpha_h i_h)[(C_{hv}\mu_h - \alpha_h\mu_v)i_h + \mu_h\mu_v](\mu_h + \gamma_h + \alpha_h)i_h = 0,$$

$$\mu_h^3 C_{vh}C_{hv}mi_h - \mu_h^2 C_{vh}C_{hv}m(\mu_h + \gamma_h + \alpha_h)i_h^2 - (\mu_h + p)[\mu_h(C_{hv}\mu_h - \alpha_h\mu_v)i_h + \mu_h^2\mu_v - \alpha_h(C_{hv}\mu_h - \alpha_h\mu_v)i_h^2$$
$$- \alpha_h\mu_v\mu_h i_h](\mu_h + \gamma_h + \alpha_h)i_h = 0,$$

$$\mu_h^3 C_{vh}C_{hv}mi_h - \mu_h^2 C_{vh}C_{hv}m(\mu_h + \gamma_h + \alpha_h)i_h^2 - (\mu_h + p)[\mu_h(\mu_h + \gamma_h + \alpha_h)(C_{hv}\mu_h - \alpha_h\mu_v)i_h^2$$
$$+ \mu_h^2\mu_v(\mu_h + \gamma_h + \alpha_h)i_h - \mu_h(\mu_h + \gamma_h + \alpha_h)\alpha_h\mu_v i_h^2 - \alpha_h(\mu_h + \gamma_h + \alpha_h)(C_{hv}\mu_h - \alpha_h\mu_v)i_h^3] = 0,$$

then

$$i_h\{\mu_h^3 C_{vh}C_{hi}m - \mu_h^2 C_{vh}C_{hv}m(\mu_h + \gamma_h + \alpha_h)i_h - (\mu_h + p)[\mu_h(\mu_h + \gamma_h + \alpha_h)(C_{hv}\mu_h - 2\alpha_h\mu_v)i_h^2$$
$$- \mu_h(\mu_h + \gamma_h + \alpha_h)i_h - \mu_h^2\mu_v(\mu_h + \gamma_h + \alpha_h)(\mu_h + p)]\} = 0,$$

i.e.

$$i_h\{(\mu_h+p)\alpha_h(\mu_h+\gamma_h+\alpha_h)(C_{hv}\mu_h-\alpha_h\mu_v)i_h^2-\mu_h(\mu_h+\gamma_h+\alpha_h)[\mu_hC_{vh}C_{hv}m+(\mu_h+p)(C_{hv}\mu_h-2\alpha_h\mu_v)]i_h + \mu_h^3C_{vh}C_{hv}m-(\mu_h+p)\mu_h^2\mu_v(\mu_h+\gamma_h+\alpha_h)\}=0,$$

$$i_h\left[\left(1+\frac{r}{\mu_h}\right)(C_{hv}\mu_h-\alpha_h\mu_v)\frac{\alpha_h}{\mu_h}i_h^2-\left[C_{vh}C_{hv}m+\left(1+\frac{r}{\mu_h}\right)(\mu_hC_{hv}-2\alpha_h\mu_v)\right]i_h + \frac{\mu_hC_{hv}C_{vh}m}{\mu_h+\gamma_h+\alpha_h}-\mu_h\mu_v\left(1+\frac{r}{\mu_h}\right)\right]=0$$

or we have

$$R=\frac{mC_{hv}C_{vh}}{\mu_v(\mu_h+\gamma_h+\alpha_h)}\Rightarrow mC_{hv}C_{vh}=\mu_v(\mu_h+\gamma_h+\alpha_h)R.$$

Therefore if we put

$$A=\left(1+\frac{r}{\mu_h}\right)[C_{hv}\mu_h-\alpha_h\mu_v]\frac{\alpha_h}{\mu_h},$$

$$B=2\left(1+\frac{r}{\mu_h}\right)\alpha_h\mu_v-\left(1+\frac{r}{\mu_h}\right)\mu_hC_{hv}-\mu_v(\mu_h+\gamma_h+\alpha_h)R,$$

$$C=\mu_h\mu_v\left(R-1-\frac{r}{\mu_h}\right),$$

then we have $i_h(Ai_h^2+Bi_h+C)=0$; therefore, the solutions of this equation are $i_h=0$ and the roots of the polynomial $f(i_h)=Ai_h^2+Bi_h+C$.

Since $s_h=\frac{\mu_h-(\mu_h+\gamma_h+\alpha_h)i_h}{\mu_h+p}\geqslant 0$ and $i_h\geqslant 0$, then

$$i_h\in\left[0,\frac{\mu_v}{\mu_h+\gamma_h+\alpha_h}\right],\quad f(0)=\mu_h\mu_v\left(R-1-\frac{r}{\mu_h}\right)$$

and

$$f\left(\frac{\mu_h}{\mu_h+\gamma_h+\alpha_h}\right)$$

$$=\frac{\alpha_h}{\mu_h}\left(1+\frac{r}{\mu_h}\right)(C_{hv}\mu_h-\alpha_h\mu_v)\frac{\mu_h^2}{(\mu_h+\gamma_h+\alpha_h)^2}-\mu_h\mu_vR+\left(2\left(1+\frac{r}{\mu_h}\right)\alpha_h\mu_v-\left(1+\frac{r}{\mu_h}\right)\mu_hC_{hv}\right) \times\frac{\mu_h}{\mu_h+\gamma_h+\alpha_h}+\mu_h\mu_v\left(R-1-\frac{r}{\mu_h}\right)=\frac{\mu_h^2}{(\mu_h+\gamma_h+\alpha_h)^2}\left[\frac{\alpha_h}{\mu_h}\left(1+\frac{r}{\mu_h}\right)(C_{hv}\mu_h-\alpha_h\mu_v) + \frac{\mu_h+\gamma_h+\alpha_h}{\mu_h}\left\{2\left(1+\frac{r}{\mu_h}\right)\alpha_h\mu_v-\left(1+\frac{r}{\mu_h}\right)\mu_hC_{hv}\right\}-\frac{\mu_h\mu_v(\mu_h+\gamma_h+\alpha_h)^2}{\mu_h^2}\left(1+\frac{r}{\mu_h}\right)\right]$$

$$=\frac{1}{(\mu_h+\gamma_h+\alpha_h)^2}\left[\alpha_h(r_h+\mu_h)(C_{hv}\mu_h-\alpha_h\mu_v)+(\mu_h+\gamma_h+\alpha_h)(2(\mu_h+p_h)\alpha_h\mu_v-\mu_h(\mu_h+p)C_{hv}) - \mu_h\mu_v(\mu_h+\gamma_h+\alpha_h)^2\left(1+\frac{r}{\mu_h}\right)\right]$$

$$=\frac{-(\mu_h+p)}{(\mu_h+\gamma_h+\alpha_h)^2}\left[C_{hv}\mu_h(\mu_h+\gamma_h)+\mu_v(\mu_h+\gamma_h)^2\right]$$

$$=\frac{-(\mu_h+p)(\mu_h+\gamma_h)}{(\mu_h+\gamma_h+\alpha_h)^2}[(\mu_h+\gamma_h)\mu_v+\mu_hC_{hv}].$$

From Eqs. (1) and (2) we obtain two equilibrium points:

(i) The first $E_1 = \left(\frac{\mu_h}{\mu_h+p}, 0, 0, 0\right)$ is trivial in the sense that all individuals are healthy and stay healthy all the time.
(ii) The second point is $E_2 = (S_h^*, I_h^*, I_v^*, n_h^*)$ which corresponds to the endemic state i.e. the case where the disease persists in the two populations.

A.2. Proof of Theorem 2

$$\frac{df_1}{ds_h} = -\mu_h - \frac{C_{vh}m}{n_h} i_v - p; \quad \frac{df_1}{di_h} = 0; \quad \frac{df_1}{di_v} = -\frac{C_{vh}m}{n_h} s_h; \quad \frac{df_1}{dn_h} = \frac{C_{vh}m}{n_h^2} i_v s_h;$$
$$\frac{df_2}{ds_h} = \frac{C_{vh}m}{n_h} i_v; \quad \frac{df_2}{di_h} = -(\mu_h + \gamma_h + \alpha_h); \quad \frac{df_2}{di_v} = \frac{C_{vh}m}{n_h} s_h; \quad \frac{df_2}{dn_h} = \frac{-C_{vh}m}{n_h^2} i_v s_h;$$
$$\frac{df_3}{ds_h} = 0; \quad \frac{df_3}{di_h} = \frac{C_{hv}}{n_h}(1 - i_v); \quad \frac{df_3}{di_v} = -\left(\frac{C_{vh} i_h}{n_h} + \mu_v\right); \quad \frac{df_3}{dn_h} = \frac{-C_{vh}}{n_h^2}(1 - i_v);$$
$$\frac{df_4}{ds_h} = 0; \quad \frac{df_4}{di_h} = -\alpha_h; \quad \frac{df_4}{di_v} = 0; \quad \frac{df_4}{dn_h} = -\mu_h.$$

(i) For E_1 the matrix of linearization (Jacobian matrix) is giving by

$$\mathcal{J}_{E_1} = \begin{pmatrix} -\mu_h - p & 0 & -\mu_h C_{vh}/\mu_h + p & 0 \\ 0 & -(\mu_h + \gamma_h + \alpha_h) & m\mu_h C_{vh}/\mu_h + p & 0 \\ 0 & C_{hv} & -\mu_v & 0 \\ 0 & -\alpha_h & 0 & -\mu_h \end{pmatrix}.$$

Then the characteristic polynomial of $\mathcal{J}_{E_1}$ is given by

$$P(\lambda) = (\mu_h + \lambda)(\mu_h + p + \lambda)\left[\lambda^2 + (\mu_h + \gamma_h + \alpha_h + \mu_v)\lambda + \mu_v(\mu_h + \gamma_h + \alpha_h)\left(1 - \frac{\mu_h}{\mu_h + p} R\right)\right].$$

Thus the eigenvalues of matrix $\mathcal{J}_{E_1}$ are: $\lambda_1 = -\mu_h$, $\lambda_2 = -(\mu_h + p)$ and the root of the polynomial

$$Q(\lambda) = \lambda^2 + (\mu_h + \gamma_h + \alpha_h + \mu_v)\lambda + \mu_v(\mu_h + \gamma_h + \alpha_h)\left(1 - \frac{\mu_h}{\mu_h + p} R\right).$$

So E_1 is stable if and only if the coefficients of polynomial Q are positive; then E_1 is stable if and only if $R < \frac{\mu_h + p}{\mu_h}$.

It remains to show the global stability, and since we have an asymptotic study we replace n_h by 1 (because $\lim_{t\to\infty} n_h(t) = 1$).

So we consider the following Liapunov function:

$$V = \frac{mC_{vh}\mu_h}{\mu_v} i_v + \frac{\mu_h + p}{\mu_h} i_h;$$

thus

$$\dot{V} = -\left(mC_{vh}\left(1 - \frac{\mu_h + p}{\mu_h} s_h\right) i_v + (\mu_h + \gamma_h + \alpha_h)\left(\frac{\mu_h + p}{\mu_h} - R + R i_v\right) i_h\right).$$

So in Ω and for $R \leqslant \frac{\mu_h + p}{\mu_h}$ we have $\dot{V} \leqslant 0$.

$$\dot{V} = 0$$
$$\Rightarrow \frac{mC_{vh}\mu_h^2}{\mu_v \Lambda_h^2}\left(\frac{\Lambda_h}{\mu_h} - \frac{\mu_h + p}{\mu_h} s_h\right) i_v + \frac{\mu_h + \gamma_h + \alpha_h}{\Lambda_h/\mu_h}\left(\frac{\mu_h + p}{\mu_h} R + R i_v\right) i_h = 0$$
$$\Rightarrow \text{If } R < \frac{\mu_h + p}{\mu_h} \text{ then } \left(\frac{\Lambda_h}{\mu_h} - \frac{\mu_h + p}{\mu_h} s_h\right) i_v = 0, \quad I_h = 0$$

and

$$\text{If } R=\frac{\mu_h+p}{\mu_h} \quad \text{then } \left(\frac{\Lambda_h}{\mu_h}-\frac{\mu_h+p}{\mu_h}S_h\right)I_v=0, I_vI_h=0.$$

Thus the set $\{E_1\}$ is the largest invariant set within the set $\{(x,y,z)/\dot{V}(x,y,z)=0\}$. So according to the invariant set theorem every trajectory in Ω tends to E_1 as time t increases and as E_1 is locally stable then it is globally asymptotically stable.

(ii) The point E_2.

The local stability of E_2 is governed by the matrix of linearization (Jacobian matrix) of E_2 is given by

$$\mathcal{J}_{E_2}=\begin{pmatrix} -\mu_h-p-\frac{mC_{vh}}{n_h}i_v & 0 & -\frac{mC_{vh}}{n_h}s_h & \frac{mC_{vh}}{n_h^2}i_vs_h \\ \frac{mC_{vh}}{n_h}i_v & -(\mu_h+\gamma_h+\alpha_h) & \frac{mC_{vh}}{n_h}s_h & \frac{-mC_{vh}}{n_h^2}i_vs_h \\ 0 & \frac{C_{hv}}{n_h}(1-i_v) & -\left(\frac{C_{hv}i_h}{n_h}+\mu_v\right) & \frac{-C_{hv}i_h}{n_h^2}(1-i_v) \\ 0 & -\alpha_h & 0 & -\mu_h \end{pmatrix},$$

or

$$\mu_h-\left(\mu_h+p+\frac{mC_{vh}}{nh}i_v\right)s_S=0\Rightarrow \mu_h+p+\frac{C_{vh}m}{n_h}i_v=\frac{\mu_h}{s_S},$$
$$\frac{mC_{vh}}{n_h}i_vs_S-(\mu_h+\gamma_h+\alpha_h)i_h=0\Rightarrow \mu_h+\gamma_h+\alpha_h=\frac{C_{vh}mi_vS_h}{n_hi_h},$$
$$\frac{C_{hv}i_h}{n_h}(1-i_v)-\mu_vi_v=0\Rightarrow \frac{C_{hv}i_h}{n_h}=\left(\frac{C_{hv}i_h}{n_h}+\mu_v\right)i_v\Rightarrow \frac{C_{hv}i_h}{n_hi_v}=\frac{C_{hv}i_h}{n_h}+\mu_v,$$

then the matrix $\mathcal{J}_{E_2}$ becomes

$$\mathcal{J}_{E_2}=\begin{pmatrix} -\frac{\mu_h}{s_h} & 0 & -\frac{mC_{vh}}{n_h}s_h & \frac{mC_{vh}}{n_h^2}i_vs_h \\ \frac{mC_{vh}}{n_h}i_v & \frac{mC_{vh}i_vs_h}{i_hn_h} & \frac{mC_{vh}}{n_h}s_h & -\frac{mC_{vh}}{n_h^2}i_vs_h \\ 0 & \frac{C_{hv}}{n_h}(1-i_v) & \frac{-C_{hv}i_h}{i_vn_h} & \frac{-C_{hv}i_h}{n_h^2}(1-i_v) \\ 0 & -\alpha_h & 0 & -\mu_h \end{pmatrix}.$$

Then the characteristic polynomial of $\mathcal{J}_{E_2}$ is given by

$$P(\lambda)=(-\mu_h-\lambda)\left[\left(\frac{-\mu_h}{s_h}-\lambda\right)\left(\frac{m\beta_h\beta_vS_h}{n_h^2}+\lambda\left(\frac{m\beta_hi_hs_h}{i_hn_h}+\frac{\beta_vi_h}{i_vn_h}\right)+\lambda^2-\frac{m\beta_h\beta_vs_h}{n_h^2}(1-i_v)\right)-\frac{m^2\beta_h^2\beta_vs_hi_v(1-i_v)}{n_h^3}\right]$$
$$-\alpha_h\left[\left(-\frac{\mu_h}{s_h}+\frac{m\beta_hi_v}{n_h}-\lambda\right)\left(-\frac{m\beta_h\beta_vi_hs_h(1-i_v)}{n_h^3}-\frac{m\beta_h\beta_vi_hs_h}{n_h^3}-\frac{m\beta_hi_vs_h}{n_h^2}\lambda\right)\right],$$

or

$$\mu_h-\frac{\beta_hm}{n_h}i_vs_h-\mu_hs_h=0\Rightarrow\frac{m\beta_hi_v}{n_h}s_h=\mu_h-\mu_hs_h\Rightarrow\frac{m\beta_hi_v}{n_h}=\frac{\mu_h}{s_h}-\mu_h$$

so

$$P(\lambda)=(-\mu_h-\lambda)\left[\left(\frac{-\mu_h}{S_h}-\lambda\right)\left(\frac{m\beta_h\beta_vs_h}{n_h^2}-\frac{m\beta_h\beta_vs_h}{n_h^2}(1-i_v)+\lambda\left(\frac{m\beta_hi_vs_h}{i_hn_h}+\frac{\beta_hi_vs_h}{i_vn_h}\right)+\lambda^2\right)\right.$$
$$\left.-\frac{m^2\beta_h^2\beta_vs_hi_v}{n_h^3}(1-i_v)\right]-\alpha_h\left[\left(\frac{-\mu_h}{s_h}+\frac{\mu_h}{s_h}-\mu_h-\lambda\right)\left(-\frac{m\beta_h\beta_vi_hs_h(1-i_v)}{n_h^3}-\frac{m\beta_h\beta_vi_hs_h}{n_h^3}-\frac{m\beta_hi_vs_h}{n_h^2}\lambda\right)\right]$$
$$=(\mu_h+\lambda)\left[\frac{\mu_h}{s_h}\frac{m\beta_h\beta_vs_h}{n_h^2}i_v+\lambda\frac{\mu_h}{s_h}\left(\frac{m\beta_hi_vs_h}{i_hn_h}+\frac{\beta_vi_h}{i_vn_h}\right)+\frac{\mu_h}{s_h}\lambda^2+\frac{m\beta_h\beta_vs_hi_v}{n_h^2}\lambda+\lambda^2\left(\frac{m\beta_hi_vs_h}{i_hn_h}+\frac{m\beta_vi_h}{i_vn_h}\right)\right.$$
$$\left.+\lambda^3+\frac{m^2\beta_h^2\beta_vs_hi_v}{n_h^2}(1-i_v)-\frac{m\beta_hi_vs_h\alpha_h\lambda}{n_h^2}-\frac{\alpha_hm\beta_h\beta_vi_hs_h(1-i_v)}{n_h^3}-\frac{\alpha_hm\beta_h\beta_vi_hs_h}{n_h^3}\right]$$
$$=(\mu_h+\lambda)\left[\lambda^3+\left(\frac{\mu_h}{s_h}+\frac{m\beta_hi_vs_h}{i_hn_h}+\frac{\beta_vi_h}{i_vn_h}\right)\lambda^2+\left\{\frac{\mu_hm\beta_hi_vs_h}{s_hi_hn_h}+\frac{\mu_h\beta_vi_h}{s_hi_vn_h}+\frac{m\beta_h\beta_vs_hi_v}{n_h}-\alpha_h\frac{m\beta_hi_vs_h}{n_h^2}\right\}\lambda\right.$$
$$\left.+\frac{\mu_hm\beta_h\beta_vi_v}{n_h^2}+\frac{m^2\beta_h^2\beta_vs_hi_v}{n_h^3}(1-i_v)-\frac{m\alpha_h\beta_h\beta_vi_hs_h}{n_h^3}(1-i_v)-\frac{\alpha_hm\beta_h\beta_vi_hs_h}{n_h^3}\right].$$

Therefore the eigenvalues of the matrix $\mathcal{J}_{E_2}$ are $-\mu_h$ and the roots of the polynomial $q(\lambda)=\lambda^3+A\lambda^2+B\lambda+C$ where

$$A=\frac{\mu_h}{s_h}+\frac{m\beta_h i_v s_h}{i_h n_h}+\frac{\beta_v i_h}{i_v n_h},$$

$$B=\frac{\mu_h\beta_v i_h}{s_h i_v n_h}+\frac{m\beta_h\beta_v s_h i_v}{n_h^2}+\frac{m\beta_h i_v(\mu_h n_h-\alpha_h i_h s_h)}{i_h n_h^2} \quad \text{and}$$

$$C=\frac{\mu_h m\beta_h\beta_v i_v}{n_h^2}+\frac{m^2\beta_h^2\beta_v s_h i_v}{n_h^3}(1-i_v)-\frac{m\alpha_h\beta_h\beta_v i_h s_h}{n_h^3}(1-i_v)-\frac{\alpha_h m\beta_h\beta_v i_h s_h}{n_h^3}.$$

Or $\alpha_h i_h=\mu_h(1-\mu_h)$ and $\frac{m\beta_h i_v}{n_h}=\frac{\mu_h-\mu_h s_h}{s_h}$. Then

$$\begin{aligned}
C&=\frac{\mu_h m\beta_h\beta_v i_v}{n_h^2}+\frac{m\beta_h^2\beta_v s_h i_v}{n_h^3}(1-i_v)+\frac{m\beta_h\beta_v s_h\mu_h}{n_h^3}(n_h-1)(1-i_v)-\frac{\alpha_h m\beta_h\beta_v i_h s_h}{n_h^3}\\
&=\frac{\mu_h m\beta_h\beta_v i_v}{n_h^2}+\frac{\mu_h m\beta_h\beta_v(1-s_h)(1-i_v)}{n_h^2}+\frac{m\beta_h\beta_v s_h\mu_h}{n_h^3}(n_h-1)(1-i_v)-\frac{\alpha_h m\beta_h\beta_v i_h s_h}{n_h^3}\\
&=\frac{\mu_h m\beta_h\beta_v i_v}{n_h^2}+\frac{\mu_h m\beta_h\beta_v(1-i_v)}{n_h^3}(n_h-ns_h+s_h n_h-s_h)-\frac{\alpha_h m\beta_h\beta_v s_h i_h}{n_h^3}\\
&=\frac{\mu_h m\beta_h\beta_v i_v}{n_h^2}+\frac{\mu_h m\beta_h\beta_v(1-i_v)(n_h-s_h)}{n_h^3}-\frac{\alpha_h m\beta_h\beta_v s_h i_h}{n_h^3}\\
&=\frac{\mu_h m\beta_h\beta_v}{n_h^3}(n_h i_v+n_h-s_h-n_h i_v+i_v s_h)-\frac{\alpha_h m\beta_h\beta_v s_h i_h}{n_h^3}=\frac{\mu_h m\beta_h\beta_v(n_h-s_h+i_v s_h)}{n_h^3}-\frac{\alpha_h m\beta_h\beta_v s_h i_h}{n_h^3}.
\end{aligned}$$

Or we have

$$\begin{aligned}
AB&=\left(\frac{\mu_h}{s_h}+\frac{m\beta_h i_v s_h}{i_h n_h}+\frac{\beta_v i_h}{i_v n_h}\right)\cdot\left(\frac{\mu_h\beta_v i_h}{s_h i_v n_h}+\frac{m\beta_h\beta_v s_h i_v}{n_h^2}+\frac{m\beta_h i_v(\mu_h n_h-\alpha_h i_h s_h)}{i_h n_h^2}\right)\\
&=\left(\frac{\mu_h}{s_h}+\frac{m\beta_h i_v s_h}{i_h n_h}\right)B+\frac{\beta_v i_h}{i_v n_h}\left(\frac{\mu_h\beta_v i_h}{s_h i_v n_h}+\frac{m\beta_h\beta_v s_h i_v}{n_h^2}\right)+\frac{m\beta_h\beta_v(\mu_h n_h-\alpha_h i_h s_h)}{n_h^3}\\
&>\frac{m\beta_h\beta_v(\mu_h n_h-\alpha_h i_h s_h)}{n_h^3}>C.
\end{aligned}$$

So $AB>C$, $A>0$, $B>0$ and $C>0$ then following the *Routh–Hurwitz* conditions for the polynomial P, the state E_2 is locally asymptotically stable for $R>\frac{\mu_h+p}{\mu_h}$.

A.3. Proof of Theorem 4

$$\frac{df_1}{ds_h}=-\mu_h-\frac{C_{vh}m}{n_h}i_v-p;\quad \frac{df_1}{di_h}=0;\quad \frac{df_1}{di_v}=-\frac{C_{vh}m}{n_h}s_h;\quad \frac{df_1}{dn_h}=\frac{C_{vh}m}{n_h^2}i_v s_h;$$

$$\frac{df_1}{dSs_h}=0;\quad \frac{df_1}{dSi_h}=0;\quad \frac{df_1}{dSn_h}=0;$$

$$\frac{df_2}{ds_h}=\frac{C_{vh}m}{n_h}i_v;\quad \frac{df_2}{di_h}=-(\mu_h+\gamma_h+\alpha_h);\quad \frac{df_2}{di_v}=\frac{C_{vh}m}{n_h}s_h;\quad \frac{df_2}{dn_h}=\frac{-C_{vh}m}{n_h^2}i_v s_h;$$

$$\frac{df_2}{dSs_h}=0;\quad \frac{df_2}{dSi_h}=0;\quad \frac{df_2}{dSn_h}=0;$$

$$\frac{df_3}{ds_h}=0;\quad \frac{df_3}{di_h}=\frac{C_{hv}}{n_h}(1-i_v);\quad \frac{df_3}{di_v}=-\left(\frac{C_{hv}i_h}{n_h}+\mu_v\right);\quad \frac{df_3}{dn_h}=\frac{-C_{hv}}{n_h^2}(1-i_v);$$

$$\frac{df_3}{dSs_h}=0;\quad \frac{df_3}{dSi_h}=\frac{C_{hv}}{n_h}(1-i_v);\quad \frac{df_3}{dSn_h}=0;$$

$$\frac{df_4}{ds_h}=0;\quad \frac{df_4}{di_h}=-\alpha_h;\quad \frac{df_4}{di_v}=0;\quad \frac{df_4}{dn_h}=-\mu_h;\quad \frac{df_4}{dSs_h}=0;\quad \frac{df_4}{dSi_h}=-\alpha_h;\quad \frac{df_4}{dSn_h}=0;$$

$$\frac{df_5}{ds_h}=-\mu_h-\frac{C_{vh}m}{n_h}i_v-p;\quad \frac{df_5}{di_h}=0;\quad \frac{df_5}{di_v}=-\frac{C_{vh}m}{n_h}s_h;\quad \frac{df_5}{dn_h}=\frac{C_{vh}m}{n_h^2}i_vs_h;$$

$$\frac{df_5}{dSs_h}=-\mu_h-\frac{C_{vh}m}{n_h}i_v-p;\quad \frac{df_5}{dSi_h}=0;\quad \frac{df_5}{dSn_h}=0;$$

$$\frac{df_6}{ds_h}=\frac{C_{vh}m}{n_h}i_v;\quad \frac{df_6}{di_h}=-(\mu_h+\gamma_h+\alpha_h);\quad \frac{df_6}{di_v}=\frac{C_{vh}m}{n_h}s_h;\quad \frac{df_6}{dn_h}=\frac{-C_{vh}m}{n_h^2}i_vs_h;$$

$$\frac{df_6}{dSs_h}=\frac{C_{vh}m}{n_h}i_v;\quad \frac{df_6}{dSi_h}=-(\mu_h+\gamma_h+\alpha_h);\quad \frac{df_6}{dSn_v}=0;$$

$$\frac{df_7}{ds_h}=0;\quad \frac{df_7}{di_h}=0;\quad \frac{df_7}{di_v}=0;\quad \frac{df_7}{dn_h}=0;\quad \frac{df_7}{dSs_h}=0;\quad \frac{df_7}{dSi_h}=-\alpha_h;\quad \frac{df_4}{dSn_h}=-\mu_h.$$

(i) For SE_1 the matrix of linearization (Jacobian matrix) has the form

$$\mathcal{J}_{SE_1}=\begin{pmatrix}J_{11} & J_{12}\\ 0 & J_{22}\end{pmatrix},$$

where

$$J_{11}=\begin{pmatrix}-\mu_h-p & 0 & -\mu_hC_{vh}/\mu_h+p & 0\\ 0 & -(\mu_h+\gamma_h+\alpha_h) & m\mu_hC_{vh}/\mu_h+p & 0\\ 0 & C_{hv} & -\mu_v & 0\\ 0 & -\alpha_h & 0 & -\mu_h\end{pmatrix},$$

$$J_{12}=\begin{pmatrix}-\mu_h-p & 0 & 0\\ 0 & -(\mu_h+\gamma_h+\alpha_h) & 0\\ 0 & -\alpha_h & -\mu_h\end{pmatrix}.$$

Thus the eigenvalues of matrix $\mathcal{J}_{E_1}$ are given by the eigenvalues of J_{11} and the eigenvalues of J_{22}.

Or the eigenvalues of J_{22} are $\lambda_1=-(\mu_h+p)$, $\lambda_2=-\mu_h$ and $\lambda_3=-(\mu_h+\gamma+\alpha_h)$. According to Theorem 2 the eigenvalues of J_{11} have a negative real part if and only if $R<\frac{\mu_h+p}{\mu_h}$. So SE_1 is stable if and only if $R<\frac{\mu_h+p}{\mu_h}$.

(ii) The point SE_2.

The local stability of SE_2 is governed by the matrix of linearization (Jacobian matrix) of SE_2; this matrix has the form:

$$\mathcal{J}_{SE_1}=\begin{pmatrix}J_{11} & J_{12}\\ 0 & J_{22}\end{pmatrix}\text{ since } Ss_h=0\quad\text{and}\quad Si_h=0,$$

where

$$J_{11}=\begin{pmatrix}-\mu_h-p-\frac{mC_{vh}}{n_h}i_v & 0 & -\frac{mC_{vh}}{n_h}s_h & \frac{mC_{vh}}{n_h^2}i_vs_h\\ \frac{mC_{vh}}{n_h}i_v & -(\mu_h+\gamma_h+\alpha_h) & \frac{mC_{vh}}{n_h}s_h & \frac{-mC_{vh}}{n_h^2}i_vs_h\\ 0 & \frac{C_{hv}}{n_h}(1-i_v) & -\left(\frac{C_{hv}i_h}{n_h}+\mu_v\right) & \frac{-C_{hv}i_h}{n_h^2}(1-i_v)\\ 0 & -\alpha_h & 0 & -\mu_h\end{pmatrix},$$

$$J_{22}=\begin{pmatrix}-\mu_h-p-\frac{mC_{vh}}{n_h}i_v & 0 & 0\\ \frac{mC_{vh}}{n_h}i_v & -(\mu_h+\gamma_h+\alpha_h) & 0\\ 0 & -\alpha_h & -\mu_h\end{pmatrix}.$$

Thus the eigenvalues of matrix $\mathcal{J}_{E_1}$ are given by the eigenvalues of J_{11} and the eigenvalues of J_{22}.

Or the eigenvalues of J_{22} are $\lambda_1 = -\left(\mu_h + p + \frac{mC_{vh}i_v}{n_h}\right)$, $\lambda_2 = -\mu_h$ and $\lambda_3 = -(\mu_h + \gamma + \alpha_h)$. According to Theorem 2 the eigenvalues of J_{11} have a negative real part if and only if $R > \frac{\mu_h+p}{\mu_h}$ so the state SE_2 is locally asymptotically stable for $R > \frac{\mu_h+p}{\mu_h}$.

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