C. R. Biologies 325 (2002) 1073–1084

S1631069102015342/FLA

Hypotheses and modelling / Hypothèses et modélisation

Threshold conditions for infection persistence in complex host-vectors interactions

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Received 26 August 2002; accepted 24 September 2002

Presented by Pierre Auger

Abstract – As classically defined by Macdonald in the early 1950s, for the case of diseases with one vector and one host, the Basic Reproduction Number, R_0, is defined as the number of secondary infections caused by a single infective of the same type (vector or host) during its infectiousness period in an entirely susceptible population. In the case of a disease which has one vector and one host, it is easy to show that R_0 coincides with the threshold for the establishment of an endemic state: if $R_0 > 1$ (< 1), the disease can invade (cannot invade) the host population. In this paper we examine various epidemic situations in which there are more than one vector and/or host. We show that in those more complex systems it is not possible to deduce a single R_0 but rather a threshold for infection persistence which is a composite of several quantities closely related to the classical expression of R_0. Another definition of R_0 given by Diekmann, Heesterbeek and Metz, and denoted in this paper R_0^{NGO} is discussed and applied as an alternative to calculate the thresholds for infection establishment. ***To cite this article: L.F. Lopez et al., C. R. Biologies 325 (2002) 1073–1084.*** © 2002 Académie des Sciences/Éditions scientifiques et médicales Elsevier SAS

basic reproductive number / vector-borne infections / yellow fever

Résumé – Conditions seuil de persistence d'infection dans un système complexe d'interactions hôte–vecteur. Dans le cas d'une infection à un seul vecteur et à un seul hôte, le taux de reproduction de base R_0 a été défini par Macdonald dans les années 1950 par le nombre d'infections secondaires causées par un seul individu infecté (hôte ou vecteur) pendant toute la durée de sa période infectueuse, au contact d'une population entièrement saine. Dans le cas d'une infection à un seul hôte et un seul vecteur, il est facile de montrer que R_0 correspond à un seuil d'installation d'un état endémique: Si $R_0 > 1$ (< 1), l'épidémie envahit (disparaît de) la population hôte. Dans cet article, nous étudions diverses situations d'épidémies à plusieurs hôtes et/ou vecteurs. Nous montrons que, dans ces systèmes plus complexes, il n'est plus possible de définir un seul R_0, mais plutôt un seuil de persistence de l'infection, qui est un agrégat de plusieurs quantités fortement connectées à l'expression classique de R_0. Nous discutons une autre définition du R_0, initialement proposée par Diekmann, Heesterbeck et Metz, notée R_0^{NGO}, qui est proposée comme une alternative pour calculer le seuil d'installation d'une infection. ***Pour citer cet article : L.F. Lopez et al., C. R. Biologies 325 (2002) 1073–1084.*** © 2002 Académie des Sciences/Éditions scientifiques et médicales Elsevier SAS

taux de reproduction de base / infection transmise par un vecteur / fièvre jaune

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1. Introduction

Often unnoticed by practicing physicians in the temperate zone, arthropod-borne diseases account for a huge proportion of the spectrum of human maladies worldwide, and the problem appears to be growing [1]. Despite the enormous effort of the medical and scientific community, controlling disease agents transmitted by arthropod vectors has proven to be difficult. The list of emerging and re-emerging infections is enormous but it is worth citing just a few: dengue, malaria, yellow fever, various mosquito-borne encephalitis, leishmaniasis, and Lyme disease.

Most of the techniques used for the control and eradication of vector-borne diseases were developed in the early 20th century. Rules for source reduction, insecticides, biological control, vaccination, chemotherapy and personal protection were all laid down nearly a century ago [2]. Many of these techniques are still effective, others succeeded initially but failed later for a variety of reasons. Investigators must now incorporate new approaches that will allow them to move to the next level of control to alleviate the effects of vector-borne diseases on human and animal health [2].

The central parameter related to the intensity of transmission of infection is the so called basic reproduction number (R_0), defined by Macdonald [3] as the number of secondary infections produced by a single infective in an entirely susceptible population (see next section). Originally applied in the context of malaria, R_0 is a function of the vector population density as related to the host population, m, the average daily biting rate of the vector, a, the host susceptibility, b, the vector mortality rate, μ, the parasite extrinsic incubation period in days, n, and the parasitemia recovery rate, r, according to the (now) historical equation:

$$R_0 = \frac{m\, a^2\, b \exp[-\mu\, n]}{r\, \mu} \qquad (1)$$

(actually, Macdonald denoted R_0 as z_0 in his original paper). From the definition of the basic reproduction number it can be demonstrated that if R_0 is not greater than one, that is, when an index case (the first infective individual) is not able to generate at least one new infection, the disease dies out. Hence, in the original Macdonald analysis, R_0 coincides with the threshold for the infection persistence. For an interesting historical account of R_0 see [4].

This paper is organized as follows. In section 2 we revisit the Macdonald analysis of malaria transmission and deduce the general expression of R_0 for any one vector – one host epidemic system. We show, using a dynamical system approach, that R_0 coincides with the threshold for the infection persistence.

In section 3 we examine the definition of the basic reproduction number given by Dieckmann, Heesterbeek and Metz [5] as compared with the classical Mcdonald analysis.

In section 4 we examine more complex vector-hosts systems, exemplifying with a 2 vectors–2 hosts system, and show that there are four basic reproduction numbers of the Macdonald type, one for each kind of index case. Obviously, those R_0's do not coincide with the threshold for epidemic persistence. However, we show that the threshold can be expressed in terms of those basic reproduction numbers. There is, however, only one basic reproduction number of the type defined by Dieckmann, Heesterbeek and Metz [5]. As we shall see the same threshold can be deduced from it.

In section 5 we discuss an even more complex epidemic system, namely the yellow fever case, which comprises three different kinds of hosts and two vectors. In this case there are five R_0's, one for each kind of index case. Also in this particular case, those R_0's do not coincide with the threshold for epidemic persistence. Again, the threshold is given by a combination of them.

Finally, in the discussion section we summarize our findings.

2. The classical Macdonald analysis

In his 1952 seminal paper, Macdonald [3] addressed the problem of a system involving one vector (*Anopheles* mosquitoes) and one host (man). As mentioned above, his definition of R_0 is the number of secondary infections in the first generation, that is, produced by a single infectee along his entire infectiousness period. We shall deduce an explicit expression for R_0 from an intuitive perspective to show that it coincides with the threshold for the establishment of the disease. We do this because, as shown in the next section for more complex systems, this approach does not work in such a simple way.

Let us begin by assuming that the index case is a human host. The question to be answered is how many human secondary infections this index case produces in his/her entire infectiousness period.

Let N_m be the number of female mosquitoes. Let a be the average daily biting rate female anophelines inflict in the human population. The number of bites in the human population per unit of time is, therefore, $N_m\, a$. Let N_h be the number of humans and r be the rate of recovery from parasitemia in the human cases. Therefore, the index case produces $\frac{N_m\, a}{N_h\, R}\, c_{h\to m}$ infected mosquitoes, where $c_{h\to m}$ is the probability that a mosquito

gets the infection after biting an infective human. These $\frac{N_m\, a}{N_h\, r}\, c_{h\to m}$ infected mosquitoes, in turn, produce $a\,\frac{N_m\, a}{N_h\, r}\, c_{h\to m}\,\frac{1}{\mu}\, b_{m\to h}\, e^{-\mu\delta}$ new human cases in the first generation, where $\frac{1}{\mu}$ is the average life expectancy of mosquitoes, $b_{m\to h}$ is the probability that a human gets the infection after being bitten by an infective mosquito and $e^{-\mu\delta}$ is the fraction of the infected mosquito population that survives through the extrinsic incubation period δ of the parasite. Note that, once infective a mosquito is assumed to remain so for life. Therefore, the expression for R_0 is [3]:

$$R_0 = a\,\frac{N_m\, a}{N_h\, r}\, c_{h\to m}\,\frac{1}{\mu}\, b_{m\to h}\, e^{-\mu\delta} \tag{2}$$

Similarly, if we begin with an infective mosquito as an index case, and compute the number of infected mosquitoes this index case produces in the first generation we get the same expression.

Let us now see how this deduction can be performed by a dynamical system approach.

Let Y_h be the number of infected humans, and Y_v the number of infected vectors. We can write

$$\frac{dY_h}{dt} = \frac{Y_v\, a}{N_h}\, b_{v\to h}\, S_h - r\, Y_h \tag{3}$$

$$\frac{dY_v}{dt} = \frac{S_v\,(t-\delta)\, a}{N_h}\, c_{h\to m}\, e^{-\mu\delta}\, Y_h\,(t-\delta) - \mu\, Y_v$$

where S_h and S_v are the number of susceptible humans and vectors, respectively.

To deduce the threshold for the disease to establish in the human population we analyse the stability of the trivial solution $S_h = N_h$, $S_v = N_v$, $Y_v = Y_h = 0$, that is, the solution representing the absence of the infection. Linearising the system (3) around the trivial solution, we get

$$\frac{dy_h}{dt} = y_v\, a\, b_{v\to h} - r\, y_h \tag{4}$$

$$\frac{dy_v}{dt} = \frac{N_v\, a}{N_h}\, c_{h\to m}\, e^{-\mu\delta}\, y_h\,(t-\delta) - \mu\, y_v$$

where y_v and y_h are small deviations from zero. From the system (4), assuming solutions of the type $y_h = A\, e^{\lambda t}$ and $y_v = B\, e^{\lambda t}$, we get the following characteristic equation for λ:

$$\begin{vmatrix} -(\lambda + r) & a\, b_{v\to h} \\ \frac{N_v\, a}{N_h}\, c_{h\to m}\, e^{-\mu\delta}\, e^{-\lambda\delta} & -(\lambda+\mu) \end{vmatrix} \tag{5}$$

or

$$\lambda^2 + (\mu + r)\,\lambda + \mu\, r - \frac{N_v\, a}{N_h}\, c_{h\to m}\, e^{-\mu\delta}\, e^{-\lambda\delta}\, a\, b_{v\to h} = 0 \tag{6}$$

It follows (see Appendix) that the roots of equation (5) or (6) have negative real parts if

$$\mu\, r - \frac{N_v\, a}{N_h}\, a\, b_{v\to h}\, c_{h\to m}\, e^{-\mu\delta} > 0 \tag{7}$$

The above result is the same as that obtained by the intuitive McDonald's approach.

This still holds true for slightly more complex systems, such as those with one vector and two hosts populations or two vectors with one host populations. In these cases, the expression for R_0 is partitioned in a sum with the individual terms of each component of the transmission chain [6].

3. The next generation operator

In a classical paper, Dieckman et al. [5] propose a new definition of the basic reproduction number for infections and we now study how it compares with the classical Macdonald definition described above.

Those authors define R_0 as being the greatest eigenvalue of an operator which they call 'the next generation operator' (NGO). The case of vector-transmitted infections was analysed in a recent book by Dieckman and Heeterbeek [7].

In this section we give the next generation operator for the case of one-vector/one-host, exemplified by malaria. In this case, the next generation operator reduces to a two-by-two matrix

$$NGO = \begin{pmatrix} A_{v\to v} & A_{v\to h} \\ A_{h\to v} & A_{h\to h} \end{pmatrix} \tag{8}$$

The elements have the following interpretation. The element $A_{v\to h}$, for instance, means the number of infected humans generated by a single infected vector during its infectious period. Therefore, we have:

$$A_{v\to v} = 0$$

$$A_{v\to h} = a\,\frac{1}{\mu}\, b_{m\to h}\, e^{-\mu\delta}$$

$$A_{h\to h} = 0$$

$$A_{h\to v} = \frac{N_m\, a}{N_h\, r}\, c_{h\to m}$$

Essentially, the NGO is the mean infectious output over all possible progressions of the infection within

the host individual and therefore contain any process that influences output of infectious material to others. In particular, the NGO was derived without appealing to the dynamical system (3).

In this case the greatest eigenvalue of the NGO matrix, that is, R_0^{NGO}, is

$$R_0^{NGO} = \sqrt{a \frac{N_m}{N_h} \frac{a}{r} c_{h\to m} \frac{1}{\mu} b_{m\to h} e^{-\mu\delta}} \qquad (9)$$

which is the square root of the Macdonald R_0. It follows from the general theory of the Next Generation Operator [5] that if $R_0^{NGO} < 1$ ($R_0^{NGO} > 1$) the disease cannot (can) invade the host population.

4. Difficulties with more complex systems

The simple one vector/one host system characteristic of a great number of vector-borne diseases such as malaria, however, is not unique in the biology of the diseases transmitted by arthropods [2].

In some cases, more than one vector, or more than one host, and in some cases, more than one parasite may be involved. Examples of the complexity of the vector-borne infections abound (see, for instance any zoonoses textbooks, for instance Palmer, Soulsby and Simpson [8]).

In some situations, several hosts may act as reservoirs of infection, being, therefore, intermediate steps in the chain of transmission. In the dengue/yellow fever complex, we have two (Haemagogus and Sabethes mosquitoes) or three (Haemagogus, Sabethes and Aedes mosquitoes) vectors for yellow fever, one common vector for dengue and yellow fever (Aedes mosquitoes), and at least two hosts (one human and one primate reservoir). As we demonstrate in the following sections, in such complex situations, a single threshold in the Macdonald's R_0 style simply does not exist.

4.1. The intuitive approach

Let us consider now a more complex system, namely one with two vectors and two host populations. This hypothetical system comprises an interaction between a human (N_h) and an animal (N_m) population, mediated by two species of vectors, referred to as (N_A) and (N_H). We shall try to deduce an explicit expression for R_0 from the intuitive perspective used by Macdonald [3].

Let us begin by assuming that there is an index case in the human population. The question to be answered is how many human and animal secondary infections this index case produces in his/her entire infectiousness period.

Let a_A be the average daily biting rate female mosquitoes of type A inflict in both host populations. The number of bites in the human population per unit of time is, therefore, $N_A\, a_A \frac{N_h}{N_h + N_m}$. Let r_h be the rate of recovery from parasitemia in the human cases. Therefore, the index case produces $N_A\, a_A \frac{N_h}{N_h + N_m} \frac{1}{N_h} \frac{1}{r_h} c_{h\to A}$ infected mosquitoes, where $\frac{1}{N_h}$ is the fraction of the bites inflicted in the index case, and $c_{h\to A}$ is the probability that a mosquito gets the infection after biting an infective human. Those $N_A\, a_A \frac{N_h}{N_h + N_m} \frac{1}{N_h} \frac{1}{r_h} c_{h\to A}$ infected mosquitoes, in turn, produce

$$N_A\, a_A \frac{N_h}{N_h + N_m} \frac{1}{N_h} \frac{1}{r_h} c_{h\to A}\, a_A \frac{1}{\mu_A} b_{A\to h} e^{-\mu_A \delta_A}$$

new human cases in the first generation, where $\frac{1}{\mu_A}$ is the average life expectancy of mosquitoes, $b_{A\to h}$ is the probability that a human gets the infection after being bitten by an infective mosquito and $e^{-\mu_A \delta_A}$ is the fraction of the infected mosquito population that survives through the extrinsic incubation period δ_A of the parasite. Note that, once infective, a mosquito is assumed to remain so for life.

By the same token, the same index case also produces

$$N_H\, a_H \frac{N_h}{N_h + N_m} \frac{1}{N_h} \frac{1}{r_h} c_{h\to H}\, a_A \frac{1}{\mu_H} b_{H\to h} e^{-\mu_H \delta_H}$$

new human cases in the first generation, through the vector population H.

On the other hand, the same human index case also produces

$$N_A\, a_A \frac{N_h}{N_h + N_m} \frac{1}{N_h} \frac{1}{r_h} c_{h\to A}\, a_A \frac{1}{\mu_A} b_{A\to m} e^{-\mu_A \delta_A}$$

secondary animal cases due to vector population of type A, and

$$N_H\, a_H \frac{N_h}{N_h + N_m} \frac{1}{N_h} \frac{1}{r_h} c_{h\to H}\, a_A \frac{1}{\mu_H} b_{H\to m} e^{-\mu_H \delta_H}$$

secondary animal cases due to vector population of type H.

Moreover, an animal index case also produces a similar amount of secondary animal and human infections due to each vector population.

Therefore, the human index case generates:

$$R_{hAh} + R_{hHh}$$

where

$$R_{\mathrm{hAh}} = N_{\mathrm{A}}\, a_{\mathrm{A}}\, \frac{N_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{h}}}\, \frac{1}{r_{\mathrm{h}}}\, c_{\mathrm{h}\to\mathrm{A}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{A}}}\, b_{\mathrm{A}\to\mathrm{h}}\, \mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}}$$

$$R_{\mathrm{hHh}} = N_{\mathrm{H}}\, a_{\mathrm{H}}\, \frac{N_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{h}}}\, \frac{1}{r_{\mathrm{h}}}\, c_{\mathrm{h}\to\mathrm{H}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{H}}}\, b_{\mathrm{H}\to\mathrm{h}}\, \mathrm{e}^{-\mu_{\mathrm{H}}\delta_{\mathrm{H}}}$$

human cases through the mosquitoes vectors A and H, respectively.

Moreover, the human index case also generates:

$$R_{\mathrm{hAm}} + R_{\mathrm{hHm}}$$

where

$$R_{\mathrm{hAm}} = N_{\mathrm{A}}\, a_{\mathrm{A}}\, \frac{N_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{h}}}\, \frac{1}{r_{\mathrm{h}}}\, c_{\mathrm{h}\to\mathrm{A}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{A}}}\, b_{\mathrm{A}\to\mathrm{m}}\, \mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}}$$

$$R_{\mathrm{hHm}} = N_{\mathrm{H}}\, a_{\mathrm{H}}\, \frac{N_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{h}}}\, \frac{1}{r_{\mathrm{h}}}\, c_{\mathrm{h}\to\mathrm{H}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{H}}}\, b_{\mathrm{H}\to\mathrm{m}}\, \mathrm{e}^{-\mu_{\mathrm{H}}\delta_{\mathrm{H}}}$$

animal cases through the mosquitoes vectors A and H, respectively.

In the case when the index case is an animal, we find that it generates:

$$R_{\mathrm{mAh}} + R_{\mathrm{mHh}}$$

where

$$R_{\mathrm{mAh}} = N_{\mathrm{A}}\, a_{\mathrm{A}}\, \frac{N_{\mathrm{m}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{m}}}\, \frac{1}{r_{\mathrm{m}}}\, c_{\mathrm{m}\to\mathrm{A}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{A}}}\, b_{\mathrm{A}\to\mathrm{h}}\, \mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}}$$

$$R_{\mathrm{mHh}} = N_{\mathrm{H}}\, a_{\mathrm{H}}\, \frac{N_{\mathrm{m}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{m}}}\, \frac{1}{r_{\mathrm{m}}}\, c_{\mathrm{m}\to\mathrm{H}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{H}}}\, b_{\mathrm{H}\to\mathrm{h}}\, \mathrm{e}^{-\mu_{\mathrm{H}}\delta_{\mathrm{H}}}$$

human cases through the mosquitoes vectors A and H, respectively.

It also generates:

$$R_{\mathrm{mAm}} + R_{\mathrm{mHm}}$$

where

$$R_{\mathrm{mAm}} = N_{\mathrm{A}}\, a_{\mathrm{A}}\, \frac{N_{\mathrm{m}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{m}}}\, \frac{1}{r_{\mathrm{m}}}\, c_{\mathrm{m}\to\mathrm{A}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{A}}}\, b_{\mathrm{A}\to\mathrm{m}}\, \mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}}$$

$$R_{\mathrm{mHm}} = N_{\mathrm{H}}\, a_{\mathrm{H}}\, \frac{N_{\mathrm{m}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{m}}}\, \frac{1}{r_{\mathrm{m}}}\, c_{\mathrm{m}\to\mathrm{H}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{H}}}\, b_{\mathrm{H}\to\mathrm{m}}\, \mathrm{e}^{-\mu_{\mathrm{H}}\delta_{\mathrm{H}}}$$

animal cases through the mosquitoes vectors A and H, respectively.

Since, strictly speaking, the expression for the basic reproduction number should be calculated starting from an index case and counting the first generation number of cases of the same kind of the index case we have two basic reproduction numbers, depending on the kind of index case.

If the index case is a human being we tentatively set

$$R_{0_{\mathrm{h}}} = R_{\mathrm{hAh}} + R_{\mathrm{hHh}}$$

On the other hand, if the index case is an animal, we tentatively set

$$R_{0_{\mathrm{m}}} = R_{\mathrm{mAm}} + R_{\mathrm{mHm}}$$

However, we still have to investigate the case where the index case is a mosquito.

Assume that the index case is a mosquito of type A. It produces

$$a_{\mathrm{A}}\, \frac{N_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{\mu_{\mathrm{A}}}\, b_{\mathrm{A}\to\mathrm{h}}$$

infected humans and

$$a_{\mathrm{A}}\, \frac{N_{\mathrm{m}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{\mu_{\mathrm{A}}}\, b_{\mathrm{A}\to\mathrm{m}}$$

animal cases. Those, in turn, produce

$$R_{\mathrm{AhA}} + R_{\mathrm{AmA}}$$

where

$$R_{\mathrm{AhA}} = N_{\mathrm{A}}\, a_{\mathrm{A}}\, \frac{N_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{m}}+N_{\mathrm{h}}}\, \frac{1}{r_{\mathrm{h}}}\, c_{\mathrm{h}\to\mathrm{A}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{A}}}\, b_{\mathrm{A}\to\mathrm{h}}\, \mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}}$$

$$R_{\mathrm{AmA}} = N_{\mathrm{A}}\, a_{\mathrm{A}}\, \frac{N_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{m}}+N_{\mathrm{h}}}\, \frac{1}{r_{\mathrm{h}}}\, c_{\mathrm{m}\to\mathrm{A}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{A}}}\, b_{\mathrm{A}\to\mathrm{m}}\, \mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}}$$

infected mosquitoes of type A.

They also produce

$$R_{\mathrm{AhH}} + R_{\mathrm{AmH}}$$

where

$$R_{\mathrm{AhH}} = N_{\mathrm{H}}\, a_{\mathrm{H}}\, \frac{N_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{m}}+N_{\mathrm{h}}}\, \frac{1}{r_{\mathrm{h}}}\, c_{\mathrm{h}\to\mathrm{H}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{A}}}\, b_{\mathrm{A}\to\mathrm{h}}\, \mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}}$$

$$R_{\mathrm{AmH}} = N_{\mathrm{H}}\, a_{\mathrm{H}}\, \frac{N_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\, \frac{1}{N_{\mathrm{m}}+N_{\mathrm{h}}}\, \frac{1}{r_{\mathrm{h}}}\, c_{\mathrm{m}\to\mathrm{H}}\, a_{\mathrm{A}}\, \frac{1}{\mu_{\mathrm{A}}}\, b_{\mathrm{A}\to\mathrm{m}}\, \mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}}$$

infected mosquitoes of type H.

So, if we stick to the convention that R_0 is the number of secondary cases of the same type of the index case, we have two more expressions:

$$R_{0_{\mathrm{A}}} = R_{\mathrm{AhA}} + R_{\mathrm{AmA}}$$

and

$$R_{0_{\mathrm{H}}} = R_{\mathrm{HhH}} + R_{\mathrm{HmH}}$$

We, therefore, have a problem. We have four tentative R_0 and we do not know if they are somehow linked with the threshold condition. Due to this fact we turn now to the dynamical system approach for the problem. First, however, we summarize and simplify our notation by defining the following transmission coefficients

$$\begin{aligned}
\beta_{\mathrm{Ah}} &= a_{\mathrm{A}} \frac{N_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}} b_{\mathrm{A}\to\mathrm{h}} \\
\beta_{\mathrm{Hh}} &= a_{\mathrm{H}} \frac{N_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}} b_{\mathrm{H}\to\mathrm{h}} \\
\beta_{\mathrm{Am}} &= a_{\mathrm{A}} \frac{N_{\mathrm{m}}}{N_{\mathrm{h}}+N_{\mathrm{m}}} b_{\mathrm{A}\to\mathrm{m}} \\
\beta_{\mathrm{Hm}} &= a_{\mathrm{H}} \frac{N_{\mathrm{m}}}{N_{\mathrm{h}}+N_{\mathrm{m}}} b_{\mathrm{H}\to\mathrm{m}} \\
\beta_{\mathrm{hA}} &= a_{\mathrm{A}} \frac{N_{\mathrm{A}}}{N_{\mathrm{h}}+N_{\mathrm{m}}} c_{\mathrm{h}\to\mathrm{A}}\, \mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}} \\
\beta_{\mathrm{mA}} &= a_{\mathrm{A}} \frac{N_{\mathrm{A}}}{N_{\mathrm{h}}+N_{\mathrm{m}}} c_{\mathrm{m}\to\mathrm{A}}\, \mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}} \\
\beta_{\mathrm{hH}} &= a_{\mathrm{H}} \frac{N_{\mathrm{A}}}{N_{\mathrm{h}}+N_{\mathrm{m}}} c_{\mathrm{h}\to\mathrm{H}}\, \mathrm{e}^{-\mu_{\mathrm{H}}\delta_{\mathrm{H}}} \\
\beta_{\mathrm{mH}} &= a_{\mathrm{H}} \frac{N_{\mathrm{A}}}{N_{\mathrm{h}}+N_{\mathrm{m}}} c_{\mathrm{m}\to\mathrm{H}}\, \mathrm{e}^{-\mu_{\mathrm{H}}\delta_{\mathrm{H}}}
\end{aligned} \tag{10}$$

Also, for future use, let us summarize the following parameters as:

$$\begin{aligned}
R_{\mathrm{hAh}} &= R_{\mathrm{AhA}} = \frac{\beta_{\mathrm{hA}}\,\beta_{\mathrm{Ah}}}{r_{\mathrm{h}}\,\mu_{\mathrm{A}}} \\
R_{\mathrm{hHh}} &= R_{\mathrm{HhH}} = \frac{\beta_{\mathrm{hH}}\,\beta_{\mathrm{Hh}}}{r_{\mathrm{h}}\,\mu_{\mathrm{H}}} \\
R_{\mathrm{mAm}} &= R_{\mathrm{AmA}} = \frac{\beta_{\mathrm{mA}}\,\beta_{\mathrm{Am}}}{r_{\mathrm{m}}\,\mu_{\mathrm{A}}} \\
R_{\mathrm{mHm}} &= R_{\mathrm{HmH}} = \frac{\beta_{\mathrm{mH}}\,\beta_{\mathrm{Hm}}}{r_{\mathrm{m}}\,\mu_{\mathrm{H}}} \\
R_{\mathrm{hHm}} &= \frac{\beta_{\mathrm{hH}}\,\beta_{\mathrm{Hm}}}{r_{\mathrm{h}}\,\mu_{\mathrm{H}}} \\
R_{\mathrm{mAh}} &= \frac{\beta_{\mathrm{mA}}\,\beta_{\mathrm{Ah}}}{r_{\mathrm{m}}\,\mu_{\mathrm{A}}} \\
R_{\mathrm{mHh}} &= \frac{\beta_{\mathrm{mH}}\,\beta_{\mathrm{Hh}}}{r_{\mathrm{m}}\,\mu_{\mathrm{H}}} \\
R_{\mathrm{hAm}} &= \frac{\beta_{\mathrm{hA}}\,\beta_{\mathrm{Am}}}{r_{\mathrm{h}}\,\mu_{\mathrm{A}}} \\
R_{\mathrm{AhH}} &= \frac{\beta_{\mathrm{Ah}}\,\beta_{\mathrm{hH}}}{r_{\mathrm{m}}\,\mu_{\mathrm{H}}} \\
R_{\mathrm{HmA}} &= \frac{\beta_{\mathrm{Hm}}\,\beta_{\mathrm{mA}}}{r_{\mathrm{m}}\,\mu_{\mathrm{H}}} \\
R_{\mathrm{AmH}} &= \frac{\beta_{\mathrm{Am}}\,\beta_{\mathrm{mH}}}{r_{\mathrm{m}}\,\mu_{\mathrm{A}}} \\
R_{\mathrm{HhA}} &= \frac{\beta_{\mathrm{Hh}}\,\beta_{\mathrm{hA}}}{r_{\mathrm{h}}\,\mu_{\mathrm{H}}}
\end{aligned} \tag{11}$$

Note also that we have

$$\begin{aligned}
R_{\mathrm{hHm}}\,R_{\mathrm{mAh}} &= R_{\mathrm{AhH}}\,R_{\mathrm{HmA}} \\
R_{\mathrm{mHh}}\,R_{\mathrm{hAm}} &= R_{\mathrm{AmH}}\,R_{\mathrm{HhA}}
\end{aligned} \tag{12}$$

Those parameters have a clear biological significance. For instance, R_{hAh} is the basic reproduction number of a human index case who generates further human infections through the infective mosquito A. Note that in R_{hAh} the mosquito population H and the population of animals m exist but are supposed not to contribute to R_{hAh}. However, the animal population appear in the parameter R_{mHm} through the factors $\frac{N_{\mathrm{H}}}{N_{\mathrm{H}}+N_{\mathrm{m}}}$ and $\frac{N_{\mathrm{A}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}$.

4.2. The dynamical system approach

The dynamical system associated with such a situation is:

$$\begin{cases}
\dfrac{\mathrm{d}Y_{\mathrm{h}}}{dt} = Y_{\mathrm{A}}\,a_{\mathrm{A}}\dfrac{S_{\mathrm{h}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\,b_{\mathrm{A}\to\mathrm{h}} \\
\qquad\qquad + Y_{\mathrm{H}}\,a_{\mathrm{H}}\dfrac{S_{\mathrm{h}}}{N_{\mathrm{h}}\,N_{\mathrm{m}}}\,b_{\mathrm{H}\to\mathrm{h}} - r_{\mathrm{h}}\,Y_{\mathrm{h}} \\
\dfrac{\mathrm{d}Y_{\mathrm{m}}}{dt} = Y_{\mathrm{A}}\,a_{\mathrm{A}}\dfrac{S_{\mathrm{m}}}{N_{\mathrm{h}}+N_{\mathrm{m}}}\,b_{\mathrm{A}\to\mathrm{m}} \\
\qquad\qquad + Y_{\mathrm{H}}\,a_{\mathrm{H}}\dfrac{S_{\mathrm{m}}}{N_{\mathrm{h}}\,N_{\mathrm{m}}}\,b_{\mathrm{H}\to\mathrm{m}} - r_{\mathrm{m}}\,Y_{\mathrm{m}} \\
\dfrac{\mathrm{d}Y_{\mathrm{A}}}{dt} = N_{\mathrm{A}}\,a_{\mathrm{A}}\dfrac{Y_{\mathrm{h}}\,(t-\delta_{\mathrm{A}})}{N_{\mathrm{h}}+N_{\mathrm{m}}}\,c_{\mathrm{h}\to\mathrm{A}}\,\mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}} \\
\qquad\qquad + N_{\mathrm{A}}\,a_{\mathrm{A}}\dfrac{Y_{\mathrm{m}}\,(t-\delta_{\mathrm{A}})}{N_{\mathrm{h}}+N_{\mathrm{m}}}\,c_{\mathrm{m}\to\mathrm{A}}\,\mathrm{e}^{-\mu_{\mathrm{A}}\delta_{\mathrm{A}}} - \mu_{\mathrm{A}}\,Y_{\mathrm{A}} \\
\dfrac{dY_{\mathrm{H}}}{dt} = N_{\mathrm{H}}\,a_{\mathrm{H}}\dfrac{Y_{\mathrm{h}}(t-\delta_{\mathrm{H}})}{N_{\mathrm{h}}+N_{\mathrm{m}}}\,c_{\mathrm{h}\to\mathrm{H}}\,\mathrm{e}^{-\mu_{\mathrm{H}}\delta_{\mathrm{H}}} \\
\qquad\qquad + N_{\mathrm{H}}\,a_{\mathrm{H}}\dfrac{Y_{\mathrm{m}}(t-\delta_{\mathrm{H}})}{N_{\mathrm{h}}+N_{\mathrm{m}}}\,c_{\mathrm{m}\to\mathrm{H}}\,\mathrm{e}^{-\mu_{\mathrm{H}}\delta_{\mathrm{H}}} - \mu_{\mathrm{H}}\,Y_{\mathrm{H}}
\end{cases} \tag{13}$$

Linearising the system (13) around the solution without disease, namely $S_{\mathrm{h}}=N_{\mathrm{h}}$, $S_{\mathrm{m}}=N_{\mathrm{m}}$, $S_{\mathrm{A}}=N_{\mathrm{A}}$, $S_{\mathrm{H}}=N_{\mathrm{H}}$, $Y_{\mathrm{h}}=Y_{\mathrm{m}}=Y_{\mathrm{A}}=Y_{\mathrm{H}}=0$, we get the following system:

$$\begin{cases}
\dfrac{\mathrm{d}y_{\mathrm{h}}}{\mathrm{d}t} = y_{\mathrm{A}}\,\beta_{\mathrm{Ah}} + y_{\mathrm{H}}\,\beta_{\mathrm{Hh}} - r_{\mathrm{h}}\,y_{\mathrm{h}} \\
\dfrac{\mathrm{d}y_{\mathrm{m}}}{\mathrm{d}t} = y_{\mathrm{A}}\,\beta_{\mathrm{Am}} + y_{\mathrm{H}}\,\beta_{\mathrm{Hm}} - r_{\mathrm{m}}\,y_{\mathrm{m}} \\
\dfrac{\mathrm{d}y_{\mathrm{A}}}{\mathrm{d}t} = y_{\mathrm{h}}(t-\delta_{\mathrm{A}})\,\beta_{\mathrm{hA}} + y_{\mathrm{m}}(t-\delta_{\mathrm{A}})\,\beta_{\mathrm{mA}} - \mu_{\mathrm{A}}\,y_{\mathrm{A}} \\
\dfrac{\mathrm{d}y_{\mathrm{H}}}{\mathrm{d}t} = y_{\mathrm{h}}(t-\delta_{\mathrm{H}})\,\beta_{\mathrm{hH}} + y_{\mathrm{m}}(t-\delta_{\mathrm{H}})\,\beta_{\mathrm{mH}} - \mu_{\mathrm{H}}\,y_{\mathrm{H}}
\end{cases} \tag{14}$$

where $y_i (i = h, m, A, H)$ are small deviations from zero. From the system (14) we get the following characteristic equation:

$$\begin{vmatrix} -(\lambda + r_h) & 0 & \beta_{Ah} & \beta_{Hh} \\ 0 & -(\lambda + r_m) & \beta_{Am} & \beta_{Hm} \\ \beta_{hA}\, e^{-\lambda\delta_A} & \beta_{mA}\, e^{-\lambda\delta_A} & -(\lambda + \mu_A) & 0 \\ \beta_{hH}\, e^{-\lambda\delta_H} & \beta_{mH}\, e^{-\lambda\delta_H} & 0 & -(\lambda + \mu_H) \end{vmatrix} = 0 \quad (15)$$

The trivial solution will then be stable if all the roots of the characteristic equation (15) have negative real parts. However, it is almost hopeless to study such a complex characteristic equation as (15), and a sensible procedure should be to neglect all the terms $e^{-\lambda\delta_i}$ $(i = A, H)$, in which case equation (15) would became a fourth order algebraic equation which can be analysed using the Routh–Hurwitz criteria [9]. This can be justified very laboriously using perturbation theory as is done for the simple case of one-host/one-parasite in the appendix. However, it is easier to apply the Next Generation Operator approach to calculate the threshold conditions for the establishment of the epidemic. This is the subject of the next section.

4.3. The next generation operator approach

For the reasons explained in the Appendix, we can neglect the time delays from the very beginning. In this case, the linearised system (14) becomes:

$$\begin{cases} \dfrac{dy_h}{dt} = y_A\, \beta_{Ah} + y_H\, \beta_{Hh} - r_h\, y_h \\ \dfrac{dy_m}{dt} = y_A\, \beta_{Am} + y_H\, \beta_{Hm} - r_m\, y_m \\ \dfrac{dy_A}{dt} = y_h\, \beta_{hA} + y_m\, \beta_{mA} - \mu_A\, y_A \\ \dfrac{dy_H}{dt} = y_h\, \beta_{hH} + y_m\, \beta_{mH} - \mu_H\, y_H \end{cases} \quad (16)$$

which can be written in the form

$$\frac{d\vec{\mathbf{y}}}{dt} = (\mathbf{T} - \mathbf{D})\, \vec{\mathbf{y}} \quad (17)$$

where **T** is a positive matrix and **D** is a diagonal positive matrix (see Dieckman and Heesterbeck [7], p. 105). The next generation operator in this case is given by a four by four matrix:

$$\mathrm{NGO} = \mathrm{TD}^{-1} = \begin{pmatrix} 0 & 0 & \dfrac{\beta_{hA}}{\mu_A} & \dfrac{\beta_{hH}}{\mu_H} \\ 0 & 0 & \dfrac{\beta_{mA}}{\mu_A} & \dfrac{\beta_{mH}}{\mu_H} \\ \dfrac{\beta_{Ah}}{r_h} & \dfrac{\beta_{Am}}{r_m} & 0 & 0 \\ \dfrac{\beta_{Hh}}{r_h} & \dfrac{\beta_{Hh}}{r_m} & 0 & 0 \end{pmatrix} \quad (18)$$

Although in this case we derived the NGO from the linearised form of the system (14), given by equation (16), this is not necessary. The NGO can be derived independently and, in particular, it does not depend on the assumption made in going from (14) to (16) of neglecting the time delays.

According to the Dieckmann et al. [5] (see also [10]) theorem, the R_0 given by the Next Generation Operator, R_0^{NGO}, is the largest eigenvalue of matrix (18). We then have

$$R_0^{NGO} = \sqrt{\frac{1}{2}\left(B + \sqrt{B^2 + 4A}\right)}$$

where

$$B = R_{AhA} + R_{HhH} + R_{AmA} + R_{HmH} = R_{hAh} + R_{hHh} + R_{mAm} + R_{mHm}$$

and

$$A = R_{hHm}\, R_{mAh} + R_{mHh}\, R_{hAm} - R_{mHm}\, R_{hAh} - R_{mAm}\, R_{hHh}$$

If $R_0^{NGO} < 1$, then the solution without disease of system (13) is stable. Therefore, the threshold condition is given, then, by

$$R_0^{NGO} = \sqrt{\frac{1}{2}\left(B + \sqrt{B^2 + 4A}\right)} \geq 1$$

which implies

$$A + B \geq 1$$

or

$$T = (1 - R_{hAh} - R_{hHh} - R_{mAm} - R_{mHm} - R_{hHm}\, R_{mAh} - R_{mHh}\, R_{hAm} + R_{mHm}\, R_{hAh} + R_{mAm}\, R_{hHh}) \leq 0 \quad (19)$$

The same conclusion can be obtained, more laboriously, by applying the Routh–Hurwitz criteria to equation (15), and taking the exponential terms $e^{-\lambda\delta_i}$ $(i = A, H)$ as 1.

Some particular cases can be analysed. Suppose that all R_{iJi} are zero except one. Then, T becomes negative if this non-zero R_{iJi} is greater than 1, and the disease can establish itself in the host population. Another more interesting case occurs when, for instance, $R_{hAh} = R_{hHh} = 0$. One might think, at first sight, that in this case a human index case cannot trigger a human epidemic. However, it can be seen that the threshold, which determines whether T is positive or negative is given by

$$T = (1 - R_{mAm} - R_{mHm} - R_{hHm}\,R_{mAh} - R_{mHh}\,R_{hAm}) \quad (20)$$

which has a simple interpretation. In this case the fourth term in the brackets, $R_{hHm}\,R_{mAh}$, describes the basic reproduction number for a human index who transmit the infection to the animal population through the mosquito type H. The infected animal then passes the disease, through mosquito type A back to the human hosts. Therefore, even when $R_{hAh} = R_{hHh} = 0$, a human index case can trigger a human epidemic. For this, it suffices that $R_{hHm}\,R_{mAh} > 1$. The other terms in the expression (20) refer to transmission among the animal population by all the possible ways and all can be less than 1 without preventing the disease establishing itself.

By the same token, if we make $R_{mAm}\,R_{mHm} = 0$ (which apparently implies that an animal index case cannot trigger an animal epidemic), then

$$T = 1 - R_{hAh} - R_{hHh} - R_{mAh}\,R_{hHm} - R_{hAm}\,R_{mHh} \quad (21)$$

which can be negative when $R_{mAh}\,R_{hHm} > 1$, even when the remaining components R_{iJi} are all less than 1.

Another attempt to interpret our condition is as follows. Suppose that when the index case is h, and $R_{mAm} = R_{mHm} = 0$. Then, we have that T reduces to (21). Suppose now that when the index case is m, and $R_{hAh} = R_{hHh} = 0$. In this case T reduces to

$$T = (1 - R_{mAm} - R_{mHm} - R_{mAh}\,R_{hHm} - R_{mHh}\,R_{hAm}) \quad (22)$$

To investigate the cases where the index cases are mosquitoes, we rewrite T using the relations given by equations (11) and (12). We get:

$$T = (1 - R_{AhA} - R_{HhH} - R_{AmA} - R_{HmH} - R_{AhH}\,R_{HmA} - R_{AmH}\,R_{HhA} + R_{HmH}\,R_{AhA} + R_{AmA}\,R_{HhH}) \quad (23)$$

If we now assume that the index cases is a mosquito of the type A, we put $R_{HhH} = R_{HmH} = 0$ to obtain

$$T = (1 - R_{AhA} - R_{AmA} - R_{AhH}\,R_{HmA} - R_{AmH}\,R_{HhA}) \quad (24)$$

Similarly, when the index case is a mosquito of type H we put $R_{AhA} = R_{AmA} = 0$ to obtain

$$T = (1 - R_{HhH} - R_{HmH} - R_{HmA}\,R_{AhH} - R_{HhA}\,R_{AmH}) \quad (25)$$

5. The yellow fever model

Urban yellow fever is transmitted from person to person by peridomestic *Aedes aegypti* mosquitoes [11]. By contrast, jungle yellow fever is a zoonosis, transmitted from monkeys to humans by mosquitoes that breed in tree-holes of the genuses Haemagogus and Sabethes in the rain forest ecosystem of South America. The jungle form is only partly controlled by vaccination of rural residents and provides a source of infection to population centres infested with *Ae aegypti*. In the early 20th century, when it was discovered that the yellow fever virus was transmitted in its urban cycle by *Aedes aegypti*, measures of control were introduced leading to its disappearance. Progressive neglect of the disease, however, led to a new outbreak in Africa in 1927 [12] during which the etiological agent was isolated; some years later a vaccine was discovered and yellow fever disappeared again. Unfortunately, reinfestation with the Aedes vector, which began in the 1970s, is now virtually complete, and vector control is substantially more difficult than before. The threat of urban yellow fever is greatest in towns near forests, but improved transport links increase the likelihood of spread by viremic people to non-endemic areas [13].

Classified as one of the viral hemorrhagic fevers, yellow fever is unique in its severity, in particular because of its hepatic impairment. Yellow fever is currently endemic and epidemic in tropical areas of the Americas and Africa [14–16].

From the point of view of its dynamics, yellow fever differs from other vector borne infection by involving three host populations and two vector populations and, therefore, as we shall see, the threshold condition for non-existence of the infection is quite complicated. We recently calculated the risk of urban yellow fever in a dengue infested area [17].

5.1. The dynamical system approach

Let $Y_c(t)$ be the number of infected human individuals living in cities, $Y_f(t)$ the number of infected 'fishermen' (those individuals who either live part of time in forest areas or who eventually frequent those areas for leisure or other purposes), $Y_m(t)$ the number of infected non-human primates, $Y_A(t)$ the number of infected mosquitoes of the Aedes genus, and $Y_H(t)$ the number of infected mosquitoes of the Haemagogus or Sabetes genuses. Let also N_i (i = c, f, m, A, H) be the total number of individuals in each population considered.

The linearised equations for Y_i around the solution without the disease are:

$$\begin{cases} \dfrac{dY_c}{dt} = Y_A\, a_A \dfrac{N_c}{N_c+N_f} b_{A\to c} - r_c\, Y_c \\ \dfrac{dY_f}{dt} = Y_A\, a_A \dfrac{N_f}{N_c+N_f} b_{A\to f} \\ \qquad + Y_H\, a_H \dfrac{N_f}{N_c+N_f} b_{H\to f} - r_f\, Y_f \\ \dfrac{dY_m}{dt} = Y_H\, a_H \dfrac{N_m}{N_m+N_f} b_{H\to m} - r_m\, Y_m \\ \dfrac{dY_A}{dt} = N_A\, a_A \dfrac{Y_c(t-\delta_A)}{N_c+N_f} g_{c\to A}\, e^{-\mu_A \delta_A} \\ \qquad + N_A\, a_A \dfrac{Y_f(t-\delta_A)}{N_m+N_f} g_{f\to A}\, e^{-\mu_A \delta_A} - \mu_A\, Y_A \\ \dfrac{dY_H}{dt} = N_H\, a_H \dfrac{Y_f(t-\delta_H)}{N_m+N_f} g_{f\to H}\, e^{-\mu_H \delta_H} \\ \qquad + N_H\, a_H \dfrac{Y_m(t-\delta_H)}{N_m+N_f} g_{m\to H}\, e^{-\mu_H \delta_H} - \mu_H\, Y_H \end{cases} \tag{26}$$

where $a_i (i = A, H)$ is the average number of bites per unit time that the vectors inflict on the hosts; $b_{i\to j}$ (i = A, H and $j = c, f$) is the fraction of the potentially infective bites ($a_i\, Y_i$) per unit time, which are actually infective; $g_{j\to i}$ (i = A, H and $j = c, f$) is the fraction of the bites inflicted on infective hosts that are really infective to the vectors. Finally, r_j (j = c, f, m) is the rate with which the hosts leave the infective compartment (either by death or by recovery from the infection), δ_i (i = A, H) is the incubation period of the virus in the mosquito population (that is, the extrinsic incubation period, the time elapsed between infection and infectiousness in the vectors) and $e^{-\mu_i \delta_i}$ is the natural mortality rate of the vectors (therefore μ_i (i = A, H) is the fraction of mosquitoes which survives throughout the extrinsic incubation period).

A few words about the system (26). Take for instance the second equation: in it, the term $Y_A\, a_A$ represents the total number of potentially infective bites Aedes mosquitoes inflict in the fraction $\dfrac{N_f}{N_c+N_f}$ of the 'fishermen' hosts, and $b_{A\to f}$ is the fraction of those bites which are actually infective for the host. Therefore, the complete term $Y_A\, a_A \dfrac{N_f}{N_c+N_f} b_{A\to f}$ is the number of 'fishermen' who get the infection per unit of time from the Aedes population. Note that we have linearised the original equations. In its complete form, the fraction $\dfrac{N_f}{N_c+N_f}$ would be $\dfrac{S_f}{N_c+N_f}$, where S_f is the number of susceptible 'fishermen'. By the same token, the second term $Y_H\, a_H \dfrac{N_f}{N_c+N_f} b_{H\to f}$ is the number of 'fishermen' who get the infection per unit of time from the Haemagogus population. And finally, the last term $r_f\, Y_f$ represents the number of 'fishermen' removed from the infectious state by death or recovery.

Similarly, the equations for the mosquitoes, for instance, the fourth equation could be explained in words as follows. The first term $N_A\, a_A$ represents the total number of bites Aedes mosquitoes inflict in the fraction $\dfrac{Y_c(t-\delta_A)}{N_c+N_f}$ of infected citizens $(t-\delta_A)$ days ago, $g_{c\to A}$ is the fraction of those bites that are actually infective for the mosquitoes, and $e^{-\mu_A \delta_A}$ is the fraction of mosquitoes that survives throughout the extrinsic incubation period, therefore becoming infective to the hosts. Therefore, the complete term $N_A\, a_A \dfrac{Y_c(t-\delta_A)}{N_c+N_f} g_{c\to A}\, e^{-\mu_A \delta_A}$ represents the number of Aedes per unit time which gets the infection from the 'citizens' hosts. Note that the original non-linearised system should be $S_A(t-\delta_A)\, a_A \dfrac{Y_c(t-\delta_A)}{N_c+N_f} g_{c\to A}\, e^{-\mu_A \delta_A}$, where $S_A(t-\delta_A)$ is the number of susceptible Aedes mosquitoes $(t-\delta_A)$ days ago. The second term of the fourth equation $N_A\, a_A \dfrac{Y_f(t-\delta_A)}{N_m+N_f} g_{f\to A}\, e^{-\mu_A \delta_A}$, by the same reasoning, represents the number of Aedes per unit time which gets the infection from the 'fishermen' hosts. And finally, the last term $\mu_A\, Y_A$ represent Aedes removed from the infective condition by mortality.

Calculating the threshold condition for yellow fever

In order to simplify the notation let us define the following transmission coefficients

$$\beta_{Ac} = a_A \frac{N_c}{N_c+N_f} b_{A\to c}$$

$$\beta_{Af} = a_A \frac{N_f}{N_c+N_f} b_{A\to f}$$

$$\beta_{Hf} = a_H \frac{N_f}{N_c+N_f} b_{H\to f}$$

$$\beta_{Hm} = a_H \frac{N_m}{N_m+N_f} b_{H\to m}$$

$$\beta_{cA} = a_A \frac{N_A}{N_c+N_f} g_{c\to A}\, e^{-\mu_A \delta_A}$$

$$\beta_{fA} = a_A \frac{N_A}{N_m+N_f} g_{f\to A}\, e^{-\mu_A \delta_A}$$

$$\beta_{fH} = a_H \frac{N_H}{N_m+N_f} g_{f\to H}\, e^{-\mu_H \delta_H}$$

$$\beta_{mH} = a_H \frac{N_H}{N_m+N_f} g_{m\to H}\, e^{-\mu_H \delta_H}$$

To calculate the threshold condition we examine the stability of the trivial solution of system (26). We get the following characteristic equation, written as a determinant:

$$\begin{vmatrix} -(r_c+\lambda) & 0 & 0 & \beta_{Ac} & 0 \\ 0 & -(r_f+\lambda) & 0 & \beta_{Af} & \beta_{Hf} \\ 0 & 0 & -(r_m+\lambda) & 0 & \beta_{Hm} \\ \beta_{cA}\,e^{-\lambda\delta_A} & \beta_{fA}\,e^{-\lambda\delta_A} & 0 & -(\mu_A+\lambda) & 0 \\ 0 & \beta_{fH}\,e^{-\lambda\delta_H} & \beta_{mH}\,e^{-\lambda\delta_H} & 0 & -(\mu_H+\lambda) \end{vmatrix} = 0 \tag{27}$$

Again, the trivial solution will then be stable if all the roots of the characteristic equation (27) have negative real parts. As mentioned above, it is almost hopeless to study such a complex characteristic equation as (27), and a sensible procedure should be to neglect all the terms $e^{-\lambda\delta_i}$ ($i = A, H$), in which case equation (27) would became a fifth order algebraic equation which can be analysed using the Routh–Hurwitz criteria [9]. This can be justified by using perturbation theory as done in the appendix. However, once again, it is easier to apply the Next Generation Operator approach to calculate the threshold conditions for the establishment of the epidemic.

5.2. The next generation operator approach

The next generation operator approach for the above model of yellow fever is given by

$$\mathrm{NGO} = \begin{pmatrix} 0 & 0 & 0 & \frac{\beta_{Ac}}{\mu_A} & 0 \\ 0 & 0 & 0 & \frac{\beta_{Af}}{\mu_A} & \frac{\beta_{Hf}}{\mu_H} \\ 0 & 0 & 0 & 0 & \frac{\beta_{Hm}}{\mu_H} \\ \frac{\beta_{cA}\,e^{-\mu_A\delta_A}}{r_c} & \frac{\beta_{fA}\,e^{-\mu_A\delta_A}}{r_f} & 0 & 0 & 0 \\ 0 & \frac{\beta_{fH}\,e^{-\mu_H\delta_H}}{r_f} & \frac{\beta_m\,e^{-\mu_H\delta_H}}{r_m} & 0 & 0 \end{pmatrix} \tag{28}$$

According to the Dieckmann et al. theorem, the R_0 given by the Next Generation Operator, R_0^{NGO}, is the largest eigenvalue of matrix (28). We then have

$$R_0^{\mathrm{NGO}} = \sqrt{\frac{1}{2}\left(B + \sqrt{B^2 + 4A}\right)}$$

where

$$B = R_{fHf} + R_{fAf} + R_{mHm} + R_{cAc}$$

and

$$A = -R_{fAf}\,R_{mHm} - R_{cAc}\,R_{mHm} - R_{cAc}\,R_{fHf}$$

The threshold condition is given, then, by

$$R_0^{\mathrm{NGO}} = \sqrt{\frac{1}{2}\left(B + \sqrt{B^2 + 4A}\right)} \geq 1$$

which implies

$$A + B \geq 1$$

or,

$$T = 1 - (R_{cAc} + R_{fAf} + R_{fHf} + R_{mHm} - R_{cAc}\,R_{fHf} - R_{cAc}\,R_{mHm} - R_{mHm}\,R_{fAf}) \leq 0$$

Some particular cases can be of interest. Suppose that transmission to fishermen is zero, that is, R_{fAf} and R_{fHf} are equal to zero. Then:

$$T = 1 - (R_{cAc} + R_{mHm} - R_{cAc}\,R_{mHm}) \leq 0 \tag{29}$$

Therefore, the threshold occurs when either R_{mHm} or R_{cAc} is greater than one. However, if both R_{mHm} and R_{cAc} are greater than one, then T may become negative. Therefore we have to apply the Routh–Hurwitz [9] condition to each particular case. However, there will obviously be an epidemic because the population of humans living in cities becomes decoupled from the population of non-human primates.

Suppose now that we have transmission only to fishermen. In this case, the threshold becomes

$$T = [1 - (R_{fAf} + R_{fHf})] \leq 0 \tag{30}$$

It is obvious that the threshold occurs when T becomes negative and is given by

$$R_{fAf} < 1 \tag{31}$$

$$R_{fHf} < 1$$

but

$$R_{fAf} + R_{fHf} > 1 \tag{32}$$

which is intuitively very reasonable.

6. Summary and discussion

The basic reproduction number, as defined by Macdonald [3] is the average number of secondary cases produced by an index case during its infectiousness period. Note that the Macdonald definition implies secondary cases of the same kind as the index case. Furthermore, the basic reproduction number in a disease which involves only one host and one vector coincides with the threshold that breaks the stability of

the trivial solution, as shown in this paper. Another definition of R_0 is the largest eigenvalue of the Next Generation Operator. The dominant eigenvalue of the NGO gives the average multiplication factor with which successive generations grow. It is therefore precisely the average number of cases in the next generation of infecteds produced by a typical case in the present generation. Thus, a threshold is immediately apparent: the disease cannot invade the population if the dominant eigenvalue of the NGO is less than 1.

Suppose now an indirectly transmitted disease which involves more than one type of host and/or vector. Then, as we have shown in this paper, several basic reproduction numbers can be defined. Notwithstanding, there is only one threshold for the epidemic persistence that can be written as a function of the many R_0's and some other quantities, which are not R_0, but are similar. In fact, they are the number of secondary cases of host(s)/vector(s) of a different kind of the index case.

In section 2, we revisited the classical Macdonald model, calculated the basic reproduction number and showed, by using a dynamical system approach, that the threshold and the R_0 are the same quantity.

In section 3, we discussed in detail the case of an hypothetical infection system with two hosts (denoted h and m) and two vectors (denoted A and H). We showed that this system has four R_0, namely

$$R_{\mathrm{hAh}} = R_{\mathrm{AhA}}$$

$$R_{\mathrm{hHh}} = R_{\mathrm{HhH}}$$

$$R_{\mathrm{mAm}} = R_{\mathrm{AmA}}$$

$$R_{\mathrm{mHm}} = R_{\mathrm{HmH}}$$

We also calculated the threshold for the epidemic persistence, which is given by a quantity T (see equation (19)), namely:

$$T = (1 - R_{\mathrm{hAh}} - R_{\mathrm{hHh}} - R_{\mathrm{mAm}} - R_{\mathrm{mHm}} - R_{\mathrm{hHh}}\,R_{\mathrm{mAh}} - R_{\mathrm{mHh}}\,R_{\mathrm{hAm}} + R_{\mathrm{mHm}}\,R_{\mathrm{hAh}} + R_{\mathrm{mAm}}\,R_{\mathrm{hHh}}) \quad (33)$$

If T is greater than zero there is no epidemic persistence. Note that T involves terms that are R_0 as defined above (like R_{hAh} or R_{hHh}), but it involves as well terms that are not R_0 but refers to the number of human or mosquitoes secondary infections produced by a single infective mosquitoe or human, respectively (like R_{hHm} or R_{mAh}).

Acknowledgements. The authors would like to thank Professor Hans Heesterbeek for his helpful comments on the manuscript. Eventual remaining errors are our own responsibility.

Appendix

We write equation (6) as:

$$\lambda^2 + a_1\,\lambda + a_{21} - a_{22}\,\mathrm{e}^{-\lambda\delta} = 0 \quad (34)$$

where

$$a_1 = \mu + r$$

$$a_{21} = \mu\, r$$

$$a_{22} = \frac{N_{\mathrm{v}}\,a}{N_{\mathrm{h}}}\,c_{\mathrm{h}\to\mathrm{m}}\,\mathrm{e}^{-\mu\,\delta}\,a\,b_{\mathrm{v}\to\mathrm{h}}$$

Assume a root

$$z = x + \mathrm{i}\,y$$

We can separate equation (34) in its real and imaginary parts. We get:

$$x^2 - y^2 + a_1\,x + a_{21} - a_{22}\,\mathrm{e}^{x\delta}\cos(y\delta) = 0 \quad (35)$$

and

$$2\,x\,y + a_1\,y - a_{22}\,\mathrm{e}^{x\delta}\sin(y\delta) = 0 \quad (36)$$

Let us solve (35) and (36) perturbatively around the solution obtained with $\delta = 0$. We write

$$x = x_0 + x_1\,\delta + x_2\,\delta^2 + \cdots \quad (37)$$

and

$$y = y_0 + y_1\,\delta + y_2\,\delta^2 + \cdots \quad (38)$$

Replacing (37) and (38) in (35) and (36), we get, keeping only terms of zero order in δ:

$$x_0^2 + a_1\,x_0 + a_{21} - a_{22} = 0 \quad (39)$$

$$2\,x_0\,y_0 + a_1\,y_0 = 0$$

whose solutions are

$$y_0 = 0$$
$$x_0 = \frac{-\,a_1 \pm \sqrt{a_1^2 - 4\,(a_{21} - a_{22})}}{2} \quad (40)$$

and

$$x_0 = -\frac{a_1}{2}$$
$$y_0 = \pm\,\frac{\sqrt{4\,(a_{21} - a_{22}) - a_1^2}}{2} \quad (41)$$

However, the second solution (41) represents a root with negative real part, and therefore is uninteresting. We can see that in the zero order in δ a root crosses the imaginary axis through the real axis when $a_{21} - a_{22} \to 0$.

The terms in first order in δ give

$$2\,x_0\,x_1 - 2\,y_0\,y_1 + a_1\,x_1 - a_{22}\,x_0 = 0 \qquad (42)$$

and

$$2\,x_0\,y_1 + 2\,x_1\,y_0 + a_1\,y_1 - a_{22}\,y_0 = 0 \qquad (43)$$

Replacing $y_0 = 0$ in equations (42) and (43), we get:

$$\begin{aligned} 2\,x_0\,x_1 + a_1\,x_1 - a_{22}\,x_0 &= 0 \\ 2\,x_0\,y_1 + a_1\,y_1 &= 0 \end{aligned} \qquad (44)$$

whose solution is

$$y_1 = 0 \qquad (45)$$

$$x_1 = \frac{a_{22}\,x_0}{2\,x_0 + a_1}$$

Then we see that when $(a_{21} - a_{22}) \to 0$, $x_1 \to 0$, together with x_0.

The terms in second order in δ, after substituting $y_0 = 0$ and $y_1 = 0$, give

$$\begin{aligned} x_1^2 + 2\,x_0\,x_2 + a_1\,x_2 - a_{22}\,x_1 - \frac{1}{2}\,a_{22}\,x_0^2 &= 0 \\ 2\,x_0\,y_2 + a_1\,y_2 &= 0 \end{aligned} \qquad (46)$$

whose solution in

$$y_2 = 0 \qquad (47)$$

$$x_2 = \frac{a_{22}\,x_1 - x_1^2 + \frac{1}{2}\,a_{22}\,x_0^2}{2\,x_0 + a_1}$$

Again we see that when $(a_{21} - a_{22}) \to 0$, $x_2 \to 0$ together with x_0 and x_1.

So, up to second order in δ, a root crosses the imaginary axis through the real axis when $(a_{21} - a_{22}) \to 0$. It is not difficult to see that all terms in the expansion vanish when $(a_{21} - a_{22}) \to 0$, showing that $a_{21} - a_{22} = 0$ is the threshold for the infection to persist.

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