IMA Journal of Mathematics Applied in Medicine and Biology (2000) **17**, 15–31

The *basic reproduction ratio* for a model of directly transmitted infections considering the virus charge and the immunological response

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[Received 28 May 1998 and in revised form 8 October 1999]

In order to describe mathematically the transmission of microparasites, especially directly transmitted infections, it is usual to set up differential equations assuming the mass action law and a homogeneously mixed population. In this paper we analyze such a model taking into account heterogeneity with respect to the infectivity, that is, the variability in the evolution of the interaction between parasite and the human host during the infectious period. The well established biological phenomenon of initial increase in parasite abundance followed by its decrease, due to the interaction between the host's immunological response and the parasite, has thus been taken into account. The variable amount of microparasites eliminated by an infectious individual, and the different (heterogeneous) immunological response build up by the host when in interaction with parasite are present in the model. The analytical expression for the *basic reproduction ratio* is derived through stability analysis.

Keywords: mathematical model; heterogeneous infectivity; amount of parasites; immunity; stability; *basic reproduction ratio*.

1. Introduction

The transmission of microparasites (specifically virus) depends on several features, as for example the environment where they circulate. Hence, favorable environmental and demographical conditions may cause an outbreak of the epidemic. The amount of circulating virus, however, depends on to the extent to which infectious individuals eliminate the harbouring virus the environment during their entire infectious period. This kind of variable (heterogeneous) infectivity during the infectious period can play an important role depending on the disease under consideration. For instance, the transmission of Human Immunodeficiency Virus (HIV) and Hepatitis Virus B (HVB) emphasizes this phenomenon due to the long and variable infectious period of these infections. Concerning childhood infections which present a short infectious period, we expect that the heterogeneous infectivity must affect their transmission to a minor degree.

In a primary viral infection in humans, the initial phase comprises population growth and the invasion of the target organ (for instance, T cells expressing surface CD4 receptors for HIV). This corresponds to a time lag of the infection when no antibody can be detected.

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Next, there is a period of rapid replication and an exponential increase in viral abundance. This increasing rate will partially depend on the efficacy of the host's immunological response. If the response is effective, antibodies and the cellular response will restrict viral population growth, such that population size decays to extinction or to very low levels. Summarizing (Anderson & May, 1991), the latent period, during which the host is infected but is not infectious due to low viral abundance, is followed by the infectious period, during which the viral abundance is high and it is eliminated to the environment. Transmission can occur when a susceptible individual comes into contact with eliminated viruses by infectious individuals. The last phase is when a host recovery occurs and the initially increased viral abundance decays to zero or to very low levels and antibody titres rise to high levels. Therefore, during the infectious period we can assume different infective capacity among the infectious individuals due to the variation in the virus abundance and the immunological response.

Also, the heterogeneous infectivity, an important biological feature related to the interaction between the immunity built up by an individual and the invading parasite, will be thought as belonging to one of two types. Firstly, we take the interaction parasite-host during the entire infectious period as being the same for all individuals. During this period we have a variable amount of virus being eliminated to the environment. However, the host-parasite interaction can be seen in another way. When humans are infected by virus, the immunological system is activated to produce a variable immunological response to eliminate the invading micro-organism. Depending on the genetic and nutritional constitution of the infected individuals, the infectious period and the efficacy of the host's immunological response may vary widely (Anderson & May, 1991).

Our goal is to assess the effects of the heterogeneous infectivity on the directly transmitted infections taking into account a variable amount of virus elimination by infectious individuals and of immunological response among the individuals. In order to do that, we developed a mathematical model and analyzed the effects of the heterogeneous infectivity on a epidemiological parameter.

In general, a mathematical model is a useful tool to quantitatively describe an epidemical phenomenon and to forecast the outcomes facing external perturbations as the vaccination strategy (Greenhalgh, 1990; Yang, 1997, 1998). An important measure which can be extracted from a mathematical model is the parameter called *basic reproduction ratio*. The estimation of this parameter is important for eradication or controlling effort (Dietz, 1993). For this reason, when sanitary authorities are dealing with an epidemic, the task of determining the *basic reproduction ratio* is a crucial point. This task depends of course on the mathematical modeling considered. In a stochastic approach, computational methods should be applied in order to assess the *basic reproduction ratio* (Robet *et al.*, 1991). In a deterministic approach (e.g., system of differential equations), analytical expression for the *basic reproduction ratio* can be obtained when simple models are considered. However, if the model takes into account more realistic considerations, e.g., the spatial or age heterogeneity, the estimation of the *basic reproduction ratio* may be feasible only through numerical calculation (Diekmann *et al.*, 1990; Greenhalgh, 1994; Inaba, 1990; Yang, 1997, 1999).

Of course, the *basic reproduction ratio* is strictly related to the assumptions considered to develop a mathematical model. In deterministic modeling of directly transmitted

infections, the concept of the *basic reproduction ratio* becomes clear when a bilinear incidence rate is assumed. This assumption is based on random encounter between susceptible and infectious individuals in a homogeneously mixed population. Nevertheless, if a non-bilinear incidence rate is assumed, then the concept of the *basic reproduction ratio* is less stringent, as this concept remains valid only for a particular value assumed by the power of the non-linearity in the incidence rate (Liu *et al.*, 1987).

This paper is structured as follows. A model dealing with variable amount of virus eliminated during the infectious period is treated in Section 2 and, in Section 3, we deal with the different immunological responses. We assume in both cases a bilinear incidence rate incorporating the heterogeneous infectivity. Stability analysis of the equilibrium establishes the analytic expression for the *basic reproduction ratio*. This formula is proved applying a finite induction principle. Finally, in Section 4, we discuss and comment our results.

2. Modeling the virus charge

After a period of time following the first infective contact with a virus, a susceptible individual builds up an immunological response. This infective period is characterized by an initial increase of the virus population followed by its decrease due to the antibody produced by the stimulated immunological system. Therefore, during this period the concentration of virus in the infectious individual varies. The shape of the curve that describes the virus charge along the infectious period follows approximately a Gaussian distribution (Anderson & May, 1991).

By applying the classical mass action law in homogeneously mixed individuals within a community, we develop a model taking into account such a variable infectiousness. This is obtained by dividing the entire infective period in k stages according to the evolution of the mechanisms of the immunological system facing the invading pathogen. The community is then divided into non-intercepting compartments describing the infection status. We are considering the compartments $S(t)$, $E(t)$, $I_j(t)$ and $R(t)$ to assign the fractions of, respectively, susceptible, exposed, j-*th* stage infectious (in a total of k) and recovered individuals.

We develop a model to describe the directly transmitted infections by considering the bilinear incidence rate and the variable amount of virus. Both assumptions, with the population subdivided into compartments according to the infection status, result in the following system of differential equations

$$\begin{cases} \frac{d}{dt}S(t) - \mu + SR(t) - \beta S(t)\sum_{j=1}^{k}\varepsilon_j I_j(t) - \mu S(t) \\ \frac{d}{dt}E(t) = \beta S(t)\sum_{j=1}^{k}\varepsilon_j I_j(t) - (\mu+\sigma)E(t) \\ \frac{d}{dt}I_1(t) = \sigma E(t) - (\mu+\gamma_1)I_1(t) \\ \frac{d}{dt}I_j(t) = \gamma_{j-1}I_{j-1}(t) - (\mu+\gamma_j)I_j(t);\ \text{for } j = 2,\ldots,k-1 \\ \frac{d}{dt}I_k(t) = \gamma_{k-1}I_{k-1}(t) - (\mu+\gamma_k)I_k(t) \\ \frac{d}{dt}R(t) = \gamma_k I_k(t) - (\mu+\delta)R(t), \end{cases} \tag{1}$$

where $S(t) + E(t) + \sum_{j=1}^{k} I_j(t) + R(t) = 1$. The parameters of the model are given

by the constants β, σ^{-1}, μ and δ, which are, respectively, the contact rate ($\beta = \beta' N$, where β' is the contact rate per person and N is the constant size of a population), the average incubation period, the mortality and the immunity loss rates. A *j-th* infective stage parameters γ_j^{-1} and ε_j are, respectively, the infectious period and the effectiveness of transmission (transmissibility) of virus. We would like to stress that the infectious period $\tau \equiv \gamma^{-1} = \sum_{j=1}^{k} \gamma_j^{-1}$ is fixed, irrespective of the number of infective stages. Here we are not considering the maternally derived antibodies and the differential mortality due to the disease.

Our aim is the establishment of a general formula for the *basic reproduction ratio* based on the stability analysis of the equilibrium points of system (1). In Subsection 2.1 we present the equilibrium points, whose stability is analyzed in Subsection 2.2.

2.1 *The equilibrium points*

The trivial equilibrium point of system (1) is given by $Q_0 = (1, 0, \ldots, 0)$, which corresponds to a disease-free population.

The unique non-trivial equilibrium point $Q = (S, E, I_1, \ldots, I_k, R)$, which corresponds to the disease at an endemic level in a community is given by

$$\begin{cases} S = \dfrac{1}{R_0} \\ E = \dfrac{(\mu+\gamma_1)(R_0-1)}{\sigma R_0\left\{1+(\mu+\gamma_1)\left[\frac{1}{\sigma}+\frac{P_k}{\mu+\delta}+\sum_{j=2}^{k}\frac{P_{j-1}}{\mu+\gamma_j}\right]\right\}} \\ I_i = \dfrac{(\mu+\gamma_1)(R_0-1)}{(\mu+\gamma_i)R_0\left\{1+(\mu+\gamma_1)\left[\frac{1}{\sigma}+\frac{P_k}{\mu+\delta}+\sum_{j=2}^{k}\frac{P_{j-1}}{\mu+\gamma_j}\right]\right\}} P_{i-1}; \text{ for } i = 1, \ldots, k \\ R = \dfrac{(\mu+\gamma_1)(R_0-1)}{(\mu+\delta)R_0\left\{1+(\mu+\gamma_1)\left[\frac{1}{\sigma}+\frac{P_k}{\mu+\delta}+\sum_{j=2}^{k}\frac{P_{j-1}}{\mu+\gamma_j}\right]\right\}} P_k, \end{cases} \tag{2}$$

where P_i will be discussed below, and the *basic reproduction ratio* R_0 is defined by

$$R_0 = \frac{\sigma}{\mu+\sigma}\sum_{l=1}^{k} P_{l-1}\frac{\beta\varepsilon_l}{\mu+\gamma_l}. \tag{3}$$

We now discuss this R_0 expression in some detail. Note first that R_0 does not depend on the loss of immunity parameter δ [14].

The first term of R_0, $\sigma/(\mu+\sigma)$, is the probability that an infected individual survives the latent period and enters the first infective stage. The term P_i, which is the probability of an individual entering the $(i+1)$-*th* stage, is defined by

$$P_i = \begin{cases} \prod_{j=1}^{i}\frac{\gamma_j}{\mu+\gamma_j}; & \text{if } i = 1, 2, \ldots, k \\ 1; & \text{if } i = 0. \end{cases}$$

Observe that $\gamma_{j-1}/(\mu+\gamma_{j-1})$ is the probability that an infectious individual survives during the $(j-1)$-*th* infective stage and enters the *j-th* infective stage. Therefore, P_i

is the survival probability from the beginning of the first infective stage up to the end of the *i-th* infective stage ($i = 1, 2, \ldots, k-1$), and P_k is the survival probability from the first infective stage until the beginning of the immunological period. Finally, $1/(\mu + \gamma_j)$ is the expected duration of the *j-th* infective stage, and $\beta\varepsilon_j$ is the rate at which secondary cases are produced during the *j-th* infectious stage.

Observe that the non-trivial equilibrium point Q is biologically viable if, and only if, we have $R_0 > 1$. The stability analysis for the equilibrium points of system (1) is performed in the next Subsection in order to establish the *basic reproduction ratio*.

2.2 *The stability analysis*

In this subsection we present the stability analysis of the trivial and non-trivial equilibrium points. For this purpose, we must evaluate the Jacobian of system (1), which is given by

$$J_{m\times m} = \begin{bmatrix} -(\beta\sum_{j=1}^{k}\varepsilon_j I_j + \mu) & 0 & -\beta\varepsilon_1 S & -\beta\varepsilon_2 S & \cdots & -\beta\varepsilon_k S & \delta \\ \beta\sum_{j=1}^{k}\varepsilon_j I_j & -(\mu+\sigma) & \beta\varepsilon_1 S & \beta\varepsilon_2 S & \cdots & \beta\varepsilon_k S & 0 \\ 0 & \sigma & -(\mu+\gamma_1) & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & -(\mu+\gamma_k) & 0 \\ 0 & 0 & 0 & 0 & \cdots & \gamma_k & -(\mu+\delta) \end{bmatrix}$$

with $m = k + 3$, at the trivial and non-trivial equilibrium points.

2.2.1 *The trivial equilibrium point.* The Jacobian evaluated at the trivial equilibrium point Q_0 results in

$$J_0 = \begin{bmatrix} -\mu & 0 & -\beta\varepsilon_1 & -\beta\varepsilon_2 & & -\beta\varepsilon_k & \delta \\ 0 & -(\mu+\sigma) & \beta\varepsilon_1 & \beta\varepsilon_2 & \cdots & \beta\varepsilon_k & 0 \\ 0 & \sigma & -(\mu+\gamma_1) & 0 & & 0 & 0 \\ & & \vdots & & \ddots & & \\ 0 & 0 & 0 & 0 & & -(\mu+\gamma_k) & 0 \\ 0 & 0 & 0 & 0 & & \gamma_k & -(\mu+\delta) \end{bmatrix} \tag{4}$$

whose eigenvalues are $\lambda_1 = -\mu$ and $\lambda_2 = -(\mu + \delta)$, plus the eigenvalues of the matrix

$$A_{n\times n} = \begin{bmatrix} -(\mu+\sigma) & \beta\varepsilon_1 & \beta\varepsilon_2 & & \beta\varepsilon_{k-1} & \beta\varepsilon_k \\ \sigma & -(\mu+\gamma_1) & 0 & \cdots & 0 & 0 \\ 0 & \gamma_1 & -(\mu+\gamma_2) & & 0 & 0 \\ & \vdots & & \ddots & & \\ 0 & 0 & 0 & & -(\mu+\gamma_{k-1}) & 0 \\ 0 & 0 & 0 & & \gamma_{k-1} & -(\mu+\gamma_k) \end{bmatrix} \tag{5}$$

with $n = k + 1$. The eigenvalues of matrix A are obtained as the roots of the characteristic polynomial

$$\Lambda_n(\lambda) = \lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n. \tag{6}$$

If we show that all eigenvalues have negative real part then the trivial equilibrium point is locally asymptotically stable.

It is well established that every root of the characteristic polynomial have negative real part if the criteria provided by Routh-Hurwitz are satisfied. However, in practice, for large values of n, these criteria are analytically nonfeasible (due to the calculations of the all minor principals of the matrix $A_{n\times n}$). Our aim is to present a simple but general criterion to assess the stability of the trivial equilibrium point Q_0. We will show that all the Routh-Hurwitz conditions can be summarized by the analysis of the λ-independent term a_n of the polynomial given by equation (6).

THEOREM 1 The trivial equilibrium point Q_0 is locally asymptotically stable (LAS) if the λ-independent term a_n of polynomial given by expression (6) is strictly positive, and unstable if a_n is strictly negative.

The proof of this theorem needs the following results.

LEMMA 1 The λ-independent term a_n of polynomial given by expression (6) can be rewritten as

$$a_n = (\mu+\sigma)\prod_{j=1}^{k}(\mu+\gamma_j) - \beta\sigma\sum_{l=1}^{k}\varepsilon_l\prod_{j=1}^{l-1}\gamma_j\prod_{m=l+1}^{k}(\mu+\gamma_m), \tag{7}$$

where $n = k+1$.

Proof. The characteristic polynomial (6) is obtained by the relation $\Lambda_n(\lambda) = \det(A-\lambda I)$. Hence, we have the λ-independent term given by $a_n = (-1)^n \det A$. □

LEMMA 2 Let us consider the $k+1$ infective stages model constructed from the k infective stages model (the order of submatrix A is $n = k+1$) by the introduction of one more infective stage. Then, the corresponding characteristic polynomial to the extended model, with order $m = k+2$, is related to the expression (6) by

$$\Lambda_m(\lambda) = (\mu+\gamma_n+\lambda)\Lambda_n(\lambda) - \beta\varepsilon_n\sigma\prod_{j=1}^{n-1}\gamma_j. \tag{8}$$

Proof. It follows by direct comparison of $\Lambda_i(\lambda) = \det(A_{i\times i} - \lambda I)$ calculated with $i = n$ and $i = n+1$. □

LEMMA 3 If the λ-independent term a_n of polynomial given by expression (6) is positive, then all a_i, $i = 1,\ldots,n-1$, are also positive.

Proof. The demonstration follows by finite induction. For $k = 1$ we have a trivial result since we have the classical *SEIRS* model, where the characteristic polynomial is given by $\Lambda_2(\lambda) = \lambda^2 + a_1\lambda + a_2$ with $a_1 > 0$ and $\tau = \gamma^{-1}$.
Now, for $k = 2$ (SEI_1I_2RS model) we have the polynomial

$$\begin{aligned}\Lambda_3(\lambda) &= (\mu+\gamma_2+\lambda)\Lambda_2'(\lambda) - \beta\varepsilon_2\sigma\gamma_1\\ &= (\mu+\gamma_2+\lambda)[(\mu+\sigma+\lambda)(\mu+\gamma_1+\lambda) - \beta\varepsilon_1\sigma] - \beta\varepsilon_2\sigma\gamma_1,\end{aligned}$$

where $\tau = \gamma_1^{-1} + \gamma_2^{-1}$, which was obtained from the expression (8) in Lemma 2. Observe that the polynomial $\Lambda_2'(\lambda)$ was obtained from $\Lambda_2(\lambda)$ of SEIRS model when we substituted γ by γ_1. Therefore, $\Lambda_2'(\lambda)$ has all the properties of $\Lambda_2(\lambda)$. In fact, if the λ-independent term of $\Lambda_3(\lambda)$ is positive, we must have

$$\begin{aligned}
&(\mu+\sigma)(\mu+\gamma_1)(\mu+\gamma_2) > \beta\varepsilon_2\sigma\gamma_1 + \beta\varepsilon_1\sigma(\mu+\gamma_2)\\
\Longleftrightarrow\ &(\mu+\sigma)(\mu+\gamma_1) > \frac{\beta\varepsilon_2\sigma\gamma_1}{(\mu+\gamma_2)} + \beta\varepsilon_1\sigma > \beta\varepsilon_1\sigma\\
\Longrightarrow\ &(\mu+\sigma)(\mu+\gamma_1) > \beta\varepsilon_1\sigma,
\end{aligned}$$

which is verified once the λ-independent term of $\Lambda_2'(\lambda)$ was assumed positive. Also, all the other coefficients of $\Lambda_3(\lambda)$ are positive, which is easily verified by inspecting the expression (8).

Finally, if we assume that the λ-independent term of $\Lambda_m(\lambda)$ is positive, where $m = k+1$, then we must have

$$(\mu+\sigma)\prod_{j=1}^{k+1}(\mu+\gamma_j') > \beta\sigma\sum_{l=1}^{k+1}\varepsilon_l\prod_{j=1}^{l-1}\gamma_j'\prod_{j=l+1}^{k+1}(\mu+\gamma_j').$$

This inequality can be modified by dividing both terms by $(\mu+\gamma_{k+1}')$ and, then, majoring the resulting expression. Hence, we have

$$(\mu+\sigma)\prod_{j=1}^{k}(\mu+\gamma_j') > \beta\sigma\sum_{l=1}^{k}\varepsilon_l\prod_{j=1}^{l-1}\gamma_j'\prod_{j=l+1}^{k}(\mu+\gamma_j'),$$

which is exactly the desired condition for the λ-independent term of $\Lambda_{m-1}'(\lambda)$. By the hypothesis of the induction, $\Lambda_{m-1}'(\lambda)$ has all coefficients positively defined. Therefore, the above inequalities plus the expression (8) show that all a_i, $i = 1, \ldots, m-1$, of $\Lambda_m(\lambda)$ are also positive. Again we have used the fact that $\Lambda_{m-1}'(\lambda)$ retains all the properties of $\Lambda_{m-1}(\lambda)$ because the former was obtained from the latter by substituting γ_i by γ_i', for $i = 1, 2, \ldots, m-2$. Note that we have $\sum_{i=1}^{m-2}\gamma_i^{-1} = \sum_{i=1}^{m-1}(\gamma_i')^{-1} = \tau$, so $\sum_{i=1}^{m-2}(\gamma_i')^{-1} < \sum_{i=1}^{m-2}\gamma_i^{-1}$. □

COROLLARY 1 If $a_n > 0$, then the polynomial $\Lambda_n(\lambda)$, defined by expression (6), is a strictly increasing function for all $\lambda \geqslant 0$.

LEMMA 4 Let $A = (a_{ij})_{1\leqslant i,j\leqslant n}$ be a real matrix with $a_{ij} \geqslant 0$ for $i \neq j$, and $\sigma(A)$ be the set of eigenvalues of A. If $\bar{\lambda} = \max\{Re(\lambda), \lambda \in \sigma(A)\}$, then $\bar{\lambda} \in \sigma(A)$. Moreover, there exists a non-zero vector $\xi \in R_+^n$ that satisfies $A\xi = \bar{\lambda}\xi$.

Proof. The demonstration follows accordingly Martin [11]. □

REMARK 1 A matrix that obeys Lemma 4 is called *quasimonotone* (see [11]).

COROLLARY 2 The matrix A given by (5) is quasimonotone and, therefore, $\bar{\lambda} = \max\{Re(\lambda), \lambda \in \sigma(A)\}$ is an eigenvalue of A. Also, the related eigenvector is non-negative.

Now we prove Theorem 1.

Proof of Theorem 1 First, we will show that $a_n > 0$ is a sufficient condition for the local stability of the trivial equilibrium point Q_0. If $a_n > 0$, then we have $a_i > 0$ (from Lemma 3), where a_i, $i = 1, \ldots, n$, are the coefficients of the polynomial given by the equation (6). Therefore, from Corollary 1, $\Lambda_n(\lambda)$ is increasing for all $\lambda \geqslant 0$. Remember that $\Lambda_n(\lambda)$ is the characteristic polynomial obtained from a quasimonotone matrix A given by (5), which implies that $\bar{\lambda} = \max\{Re(\lambda), \lambda \in \sigma(A)\}$ is an eigenvalue of A, i.e., the dominant eigenvalue of A is a real number (from Lemma 4 and Corollary 2). Observing that $\Lambda_n(0) = a_n > 0$, we must have $\bar{\lambda} < 0$, which implies that $Re(\lambda) < 0$ for all $\lambda \in \sigma(A)$. Hence the trivial equilibrium point Q_0 is LAS.
Conversely, if Q_0 is LAS, then we must have $Re(\lambda) < 0$ for all $\lambda \in \sigma(A)$. Moreover, the λ-independent term of $\Lambda_n(\lambda)$, calculated from $a_n = (-1)^n \det A$, that is,

$$a_n = (-1)^n \prod_{i=1}^{n} \lambda_i; \quad \lambda_i \in \sigma(A),$$

is always positive for all $n \in N$, due to $Re(\lambda_i) < 0$, for $i = 1, 2, \ldots, n$. This result remains valid if we have complex roots, since they appear in pairs.

From the above results we state the following theorem.

THEOREM 2 The basic reproduction ratio R_0 related to system of equation (1) is given by formula (3), i.e.,

$$R_0 = \frac{\sigma}{\mu + \sigma} \sum_{l=1}^{k} P_{l-1} \frac{\beta \varepsilon_l}{\mu + \gamma_l}.$$

Proof. The expression for a_n (see Lemma 1) is positive, if and only if,

$$(\mu + \sigma) \prod_{j=1}^{k} (\mu + \gamma_j) > \beta\sigma \sum_{l=1}^{k} \varepsilon_l \prod_{j=1}^{l-1} \gamma_j \prod_{m=l+1}^{k} (\mu + \gamma_m)$$

$$\Longleftrightarrow \frac{\mu + \sigma}{\beta\sigma} > \sum_{l=1}^{k} P_{l-1} \frac{\varepsilon_l}{\mu + \gamma_l}$$

$$\Longleftrightarrow \frac{\beta\sigma}{\mu + \sigma} \sum_{l=1}^{k} P_{l-1} \frac{\varepsilon_l}{\mu + \gamma_l} < 1.$$

Observe that if we have $R_0 > 1$, then the trivial equilibrium point is unstable. Therefore, at $R_0 = 1$ we have the transition from the disease-free population to the infection at an endemic level in the community. □

THEOREM 3 If the trivial equilibrium point Q_0 is LAS then it is globally asymptotically stable (GAS).

Proof. Since the relation $S + E + I_1 + \cdots + I_k + R = 1$ is valid for the system of equations (1), it can be rewritten as

$$\frac{dy}{dt} = By + G(y), \tag{9}$$

where $y = (E, I_1, \ldots, I_k, R)^T$, B is the Jacobian matrix corresponding to system (9), which is given by

$$B = \begin{bmatrix} -(\mu+\sigma) & \beta\varepsilon_1 & \beta\varepsilon_2 & & \beta\varepsilon_k & 0 \\ \sigma & -(\mu+\gamma_1) & 0 & \cdots & 0 & 0 \\ 0 & \gamma_1 & -(\mu+\gamma_2) & & 0 & 0 \\ & \vdots & & \ddots & & \\ 0 & 0 & 0 & & -(\mu+\gamma_k) & 0 \\ 0 & 0 & 0 & & \gamma_k & -(\mu+\delta) \end{bmatrix},$$

and the vector $G(y)$ is the non-linear part given by

$$G(y) = \left(-\beta[E + I_1 + \cdots + I_k + R]\sum_{j=1}^{k}\varepsilon_j I_j, 0, \ldots, 0\right)^T.$$

The superscript T stands for the transposition of matrix. Note that matrix B is equal to matrix J_0, given by (4), except for the first row and the first column.
The matrix B^T is quasimonotone and there exists an eigenvector $w^* = (w_1, \ldots, w_{k+2})^T$ with non-negative coordinates related to an eigenvalue $\bar{\lambda} < 0$ (see Lemma 4). In this case, we must have $w_i^* > 0$ for all $i = 1, \ldots, k+2$. In fact, from $B^T w^* = \bar{\lambda} w^*$ we can obtain

$$\begin{cases} 0 \leqslant w_2 \leqslant \frac{\mu+\sigma}{\sigma} w_1 \\ \text{and} \\ 0 \leqslant w_{i+2} \leqslant \frac{(\mu+\gamma_i)w_{i+1} - \beta\varepsilon_i w_1}{\gamma_i}; \quad \text{for } i = 1, \ldots, k. \end{cases}$$

If $w_1 = 0$ then $w^* = 0$, which is a contradiction. Assuming that $w_1 > 0$ and $w_{i+1} = 0$ for some i then we have $w_{i+2} < 0$, which is also a contradiction. Therefore, the eigenvector w^* is strictly positive.
Considering the Liapunov function given by $V(y) = w^* \cdot y$, then the hypotheses of Theorem 4.2 of Lajmanovich and Yorke [9] are satisfied and, therefore, the trivial equilibrium point is GAS. □

COROLLARY 3 The necessary and sufficient conditions for the non-trivial equilibrium point Q to be biologically viable is $a_n < 0$.

In the next subsection we will deal with the stability of the non-trivial equilibrium point.

2.2.2 *The non-trivial equilibrium point.* The Jacobian evaluated at the non-trivial equilibrium point Q,

$$J = \begin{bmatrix} -\left(\beta\sum_{j=1}^{k}\varepsilon_j I_j + \mu\right) & 0 & -\beta\varepsilon_1 S & -\beta\varepsilon_2 S & & -\beta\varepsilon_k S & \delta \\ \beta\sum_{j=1}^{k}\varepsilon_j I_j & -(\mu+\sigma) & \beta\varepsilon_1 S & \beta\varepsilon_2 S & \cdots & \beta\varepsilon_k S & 0 \\ 0 & \sigma & -(\mu+\gamma_1) & 0 & & 0 & 0 \\ & \vdots & & & \ddots & & \\ 0 & 0 & 0 & 0 & & -(\mu+\gamma_k) & 0 \\ 0 & 0 & 0 & 0 & & \gamma_k & -(\mu+\delta) \end{bmatrix},$$

has its corresponding characteristic polynomial given by

$$\Lambda(\lambda) = \lambda^{k+3} + a_1\lambda^{k+2} + \cdots + a_{k+2}\lambda + a_{k+3}.$$

After massive calculations, the λ-independent term of $\Lambda(\lambda)$ is obtained as

$$a_{k+3} = (-1)^{k+3} \det J = C(R_0 - 1), \tag{10}$$

where the positively defined C is

$$C = \frac{\mu D(\mu+\sigma)(\mu+\gamma_1)}{\sigma} \prod_{j=1}^{k}(\mu+\gamma_j)\left\{\mu+\sigma+\delta\left[1+\sigma\sum_{l=1}^{k} P_{l-1}\frac{1}{\mu+\gamma_l}\right]\right\},$$

with

$$D = \left[1+(\mu+\gamma_1)\left(\frac{1}{\sigma}+\frac{1}{\mu+\delta}P_k+\sum_{i=2}^{k}\frac{P_{i-1}}{\mu+\gamma_i}\right)\right]^{-1}.$$

We note that $R_0 > 1$ is the necessary and sufficient condition for $a_{k+3} > 0$. In previous Subsection, we have demonstrated the instability of the trivial equilibrium point Q_0 and the biologically viability of the non-trivial equilibrium point Q. We state the following conjecture.

CONJECTURE 1 The condition $a_{k+3} > 0$ is necessary and sufficient for the non-trivial equilibrium point Q be LAS.

The rationale behind the Conjecture 1 is as follows. We have proved (Theorems 1 and 3) that the stability conditions for the trivial equilibrium point can be obtained by the sole evaluation of the independent term of the characteristic polynomial a_n. Observe that the assumption for the non-trivial equilibrium point Q, that is, $a_{k+3} > 0$, is true if we have $R_0 > 1$, and, for this reason, the Conjecture 1 states that all the Routh-Hurwitz conditions are satisfied.

3. Modeling the immunological response

As we have pointed out previously, when a susceptible individual has the first infective contact with virus, this individual builds up an immunological response after a certain period of time. Also, this infective period is characterized by the abundance of the initial virus rising followed by its later decreasing due to the antibodies produced by the stimulated immunological system which destroys completely (or at a very low level) the invading pathogens. In the previous Section, we did not take into account the heterogeneity among individuals. However, the genetic and nutritional aspects of the infected individual can affect both the infectious period and the virus charge.

As in the preceding Section, we apply the classical mass action law to a homogeneously mixed population to develop a model considering a heterogeneous immunological response. This is obtained by dividing the entire latent individuals into k different infection status classes according to their immunological response to the virus.

The bilinear incidence model encompassing the heterogeneous immunological response and describing directly transmitted infection can now be set in terms of the fraction of individuals in each class as

$$\begin{cases} \frac{\mathrm{d}}{\mathrm{d}t}S(t) = \mu + \delta R(t) - \beta S \sum_{j=1}^{k} \varepsilon_j I_j(t) - \mu S(t) \\ \frac{\mathrm{d}}{\mathrm{d}t}E(t) = \beta S(t) \sum_{j=1}^{k} \varepsilon_j I_j(t) - (\mu + \sigma)E(t) \\ \frac{\mathrm{d}}{\mathrm{d}t}I_j(t) = f_j \sigma E(t) - (\mu + \gamma_j)I_j(t); \text{ for } j = 1, \ldots, k \\ \frac{\mathrm{d}}{\mathrm{d}t}R(t) = \sum_{j=1}^{k} \gamma_j I_j(t) - (\mu + \delta)R(t), \end{cases} \tag{11}$$

where $S(t) + E(t) + \sum_{j=1}^{k} I_j(t) + R(t) = 1$, which are, respectively, the fractions of susceptible, exposed, *j-th* infective (in a total of k) and recovered individuals. The constants β, σ^{-1}, μ and δ, were defined in the preceding Section. The parameters γ_j^{-1} and ε_j are, respectively, the infectious period and the effectiveness of the transmission of the *j-th* infection status, and f_j is the proportion of exposed individuals that goes to the *j-th* infection status. Clearly we have $\sum_{j=1}^{k} f_j = 1$.

For this model, we obtain a general formula for the *basic reproduction ratio* based on the stability analysis of the equilibrium points of system (11). In Subsection 3.1 we present the equilibrium points, whose stability is analyzed in Subsection 3.2.

3.1 *The equilibrium points*

The trivial equilibrium point of system of equations (11) is given by $Q_0 = (1, 0, \ldots, 0)$, which corresponds to a disease-free population.

The unique non-trivial equilibrium point $Q = (S, E, I_1, \ldots, I_k, R)$ corresponding to the disease at an endemic level in a community is given by

$$\begin{cases} S = \dfrac{1}{R_0} \\ E = \dfrac{R_0 - 1}{R_0\left[1 + \sigma \sum_{i=1}^{k} f_i \left(\frac{1}{\mu+\gamma_i} + \frac{1}{\mu+\delta} \times \frac{\gamma_i}{\mu+\gamma_i}\right)\right]} \\ I_j = f_j \dfrac{(R_0 - 1)\sigma}{R_0(\mu + \gamma_j)\left[1 + \sigma \sum_{i=1}^{k} f_i \left(\frac{1}{\mu+\gamma_i} + \frac{1}{\mu+\delta} \times \frac{\gamma_i}{\mu+\gamma_i}\right)\right]}; \text{ for } j = 1, \ldots, k \\ R = \dfrac{(R_0 - 1)\sigma}{R_0(\mu + \delta)\left[1 + \sigma \sum_{i=1}^{k} f_i \left(\frac{1}{\mu+\gamma_i} + \frac{1}{\mu+\delta} \times \frac{\gamma_i}{\mu+\gamma_i}\right)\right]} \sum_{i=1}^{k} f_i \dfrac{\gamma_i}{\mu + \gamma_i}, \end{cases} \tag{12}$$

where the *basic reproduction ratio* R_0 is defined by

$$R_0 = \frac{\sigma}{\mu + \sigma} \sum_{j=1}^{k} f_j \frac{\beta \varepsilon_j}{\mu + \gamma_j}. \tag{13}$$

Again, observe that R_0 does not depend on the loss of immunity parameter δ.

The first term of R_0, $\sigma/(\mu + \sigma)$, is the probability that an infected individual survives the latent period and enters to one of the k different infection status classes. The term

$1/(\mu+\gamma_j)$ is the expected duration of the *j-th* infection status, and $\beta\varepsilon_j$ is the rate at which secondary cases are produced during the *j-th* infection status. Finally, f_j is the contribution of the *j-th* infection status.

Observe that Q is biologically viable if, and only if, we have $R_0 > 1$. The stability analysis of the trivial equilibrium point of system (11) is performed in the next subsection in order to establish the *basic reproduction ratio.*

3.2 *The stability analysis*

In this Section we present the stability analysis of the trivial and non-trivial equilibrium points.

The Jacobian of system (11) is given by

$$J_{m\times m}=\begin{bmatrix} -\left(\beta\sum_{j=1}^{k}\varepsilon_j I_j+\mu\right) & 0 & -\beta\varepsilon_1 S & -\beta\varepsilon_2 S & \cdots & -\beta\varepsilon_k S & \delta \\ \beta\sum_{j=1}^{k}\varepsilon_j I_j & -(\mu+\sigma) & \beta\varepsilon_1 S & \beta\varepsilon_2 S & \cdots & \beta\varepsilon_k S & 0 \\ 0 & f_1\sigma & -(\mu+\gamma_1) & 0 & \cdots & 0 & 0 \\ & f_2\sigma & 0 & -(\mu+\gamma_2) & & 0 & 0 \\ \vdots & \vdots & \vdots & & \ddots & \vdots & \vdots \\ 0 & f_k\sigma & 0 & 0 & \cdots & -(\mu+\gamma_k) & 0 \\ 0 & 0 & \gamma_1 & \gamma_2 & \cdots & \gamma_k & -(\mu+\delta) \end{bmatrix}$$

with $m = k + 3$. This matrix is evaluated at the trivial and non-trivial equilibrium points.

3.2.1 *The trivial equilibrium point.* The Jacobian evaluated at the trivial equilibrium point Q_0 results in

$$J_0=\begin{bmatrix} -\mu & 0 & -\beta\varepsilon_1 & -\beta\varepsilon_2 & & -\beta\varepsilon_k & \delta \\ 0 & -(\mu+\sigma) & \beta\varepsilon_1 & \beta\varepsilon_2 & \cdots & \beta\varepsilon_k & 0 \\ 0 & f_1\sigma & -(\mu+\gamma_1) & 0 & & 0 & 0 \\ 0 & f_2\sigma & 0 & -(\mu+\gamma_2) & & 0 & 0 \\ & & \vdots & & \ddots & & \\ 0 & f_k\sigma & 0 & 0 & & -(\mu+\gamma_k) & 0 \\ 0 & 0 & \gamma_1 & \gamma_2 & & \gamma_k & -(\mu+\delta) \end{bmatrix}, \tag{14}$$

and the corresponding eigenvalues are $\lambda_1 = -\mu$ and $\lambda_2 = -(\mu+\delta)$, plus the eigenvalues of the matrix

$$A_{n\times n}=\begin{bmatrix} -(\mu+\sigma) & \beta\varepsilon_1 & \beta\varepsilon_2 & & \beta\varepsilon_{k-1} & \beta\varepsilon_k \\ f_1\sigma & -(\mu+\gamma_1) & 0 & \cdots & 0 & 0 \\ f_2\sigma & 0 & -(\mu+\gamma_2) & & 0 & 0 \\ & \vdots & & \ddots & & \\ f_{k-1}\sigma & 0 & 0 & & -(\mu+\gamma_{k-1}) & 0 \\ f_k\sigma & 0 & 0 & & 0 & -(\mu+\gamma_k) \end{bmatrix} \tag{15}$$

with $n = k + 1$. The eigenvalues of matrix A are obtained as the roots of the characteristic polynomial

$$\Lambda(\lambda)=(\mu+\sigma+\lambda)\prod_{i=1}^{k}(\mu+\gamma_i+\lambda)-\sigma\beta\sum_{j=1}^{k}f_j\varepsilon_j\left[\prod_{i=1,i\neq j}^{k}(\mu+\gamma_i+\lambda)\right]. \tag{16}$$

THEOREM 4 The trivial equilibrium point Q_0 is LAS if the λ-independent term a_n of polynomial given by expression (16) is strictly positive, and unstable if a_n is strictly negative.

The proof of this theorem needs the following results.

LEMMA 5 The λ-independent term a_n of the characteristic polynomial given by expression (16) can be rewritten as

$$a_n = (\mu+\sigma)\prod_{j=1}^{k}(\mu+\gamma_j) - \beta\sigma\sum_{j=1}^{k} f_j\varepsilon_j \prod_{i=1, i\neq j}^{k}(\mu+\gamma_i), \tag{17}$$

where $n = k+1$.

Proof. From the fact that the polynomial given by equation (16) comes from $\Lambda(\lambda) = \det(A - \lambda I)$, we have the λ-independent term given by $a_n = (-1)^n \det A$. □

LEMMA 6 All the eigenvalues of matrix A are real.

Proof. From the expression (16), we observe that the characteristic roots are the same as for the equation

$$\Lambda(\lambda) = -(\mu+\sigma+\lambda) + \sigma\beta\sum_{j=1}^{k}\frac{f_j\varepsilon_j}{\mu+\gamma_j+\lambda}, \tag{18}$$

with $\lambda \neq (\mu+\gamma_j)$, for $j = 1, \ldots, k$.
If we suppose that $\lambda = a + bi$ is a complex eigenvalue, then we must have the identity

$$-b\sum_{j=1}^{k}\frac{f_j\varepsilon_j}{(\mu+\gamma_j+a)^2+b^2} = \frac{b}{\sigma\beta}.$$

But, the expression is valid only if we have $b = 0$. Therefore, all the eigenvalues are real. □

Now we prove Theorem 4.

Proof of Theorem 4 Let us consider $a_n > 0$ and, by contradiction, suppose that there is an eigenvalue $\lambda > 0$. Then $\Lambda(\lambda) = 0$ and, by equation (18), λ must satisfy

$$\mu+\sigma+\lambda = \sigma\beta\sum_{j=1}^{k}\frac{f_j\varepsilon_j}{\mu+\gamma_j+\lambda}.$$

By the assumption that $\lambda > 0$, we must have

$$\mu+\sigma < \mu+\sigma+\lambda = \sigma\beta\sum_{j=1}^{k}\frac{f_j\varepsilon_j}{\mu+\gamma_j+\lambda} < \sigma\beta\sum_{j=1}^{k}\frac{f_j\varepsilon_j}{\mu+\gamma_j}.$$

This implies that $\mu + \sigma < \sigma\beta \sum_{j=1}^{k} \frac{f_j \varepsilon_j}{\mu+\gamma_j}$. This inequality is equivalent to $a_n < 0$, which is a contradiction.

On the other hand, let us suppose that all eigenvalues λ are strictly negative and suppose now that $a_n < 0$. This implies that the polynomial

$$\Lambda(\lambda) = (\mu + \sigma + \lambda)\prod_{i=1}^{k}(\mu + \gamma_i + \lambda) - \sigma\beta \sum_{j=1}^{k} f_j \varepsilon_j \left[\prod_{i=1, i\neq j}^{k} (\mu + \gamma_i + \lambda) \right]$$

is strictly negative at $\lambda = 0$ and tends to infinity as $\lambda \to \infty$. Hence it has at least one positive root, which is a contradiction.

Therefore, the trivial equilibrium point is LAS if $a_n > 0$ and is unstable if $a_n < 0$.

We note that the condition $a_n > 0$ is equivalent to $R_0 < 1$. Therefore, we can assure that the trivial equilibrium point is LAS if $R_0 < 1$.

4. Discussion

First, we developed a mathematical model taking into account a heterogeneous infectivity based on virus charge harboured by human hosts. From this model, we determined the formula for the *basic reproduction ratio*, when the infectious individuals were subdivided into k infective stages according to the interaction between the host's immunological response and the virus.

The formula (3) for the *basic reproduction ratio* was obtained by analyzing the stability of the trivial equilibrium point of system (1), and we demonstrated that the stability results can be assessed by analyzing the λ-independent term of the characteristic polynomial, for instance, that one provided by equation (7). We conjectured that the non-trivial equilibrium point must be locally asymptotically stable if the *basic reproduction ratio* assumes a value above unity.

The *basic reproduction ratio* for the classical SEIRS model can be obtained from formula (3) by letting $k = 1$, resulting in

$$R_0 = \frac{\sigma}{\mu + \sigma} \times \frac{\beta}{\mu + \gamma},$$

where we have used the substitutions $\gamma_1 = \gamma$, $P_0 = 1$ and $\varepsilon_1 = 1$. Observe that the general formula (3) for the *basic reproduction ratio* is the sum of k sequentially infective stages through which the infectious individuals passed. For this reason, note that this formula depends on the probability P_{i-1}, which is lower than unity and is strongly related to the $(i-1)$-*th* infective stage. The reason is that this probability considers the survival of the infectious individuals until the $(i-1)$-*th* infective stage, and the posterior entrance into the i-*th* infective stage. Note that if we do not consider the mortality rate, than we must have $P_{i-1} = 1$, for all i. If we consider a mortality rate that appropriately describes the developed countries, as for example, $\mu(a) = 0$, for $a < L$, and $\mu(a) = \infty$, otherwise, where L can be the life expectancy (Anderson & May, 1991), then we have $P_i = 1$, for all i. Therefore, the heterogeneity in the viral burden can be summarized by

$$R_0 = \beta \sum_{l=1}^{k} \frac{\varepsilon_l}{\gamma_l},$$

which depends on the transmissibility of virus (ε_l) and the infectious rate (γ_l) of the *l-th* infective stage.

A more elaborate model considering the heterogeneous infectivity is proposed by Jacquez *et al.* (1988). In their model, the highly variable course of infection and progression to AIDS have been taken into account, where susceptible individuals, once infected, pass through a series of infectious stages. In that case the period from infection up to the appearance of the first symptoms has been estimated to have a mean of 4.5 to 8 or more years. They calculated the endemicity threshold in the case of restricted mixing. We can relate their *basic reproduction ratio* to the expression (3) provided by the model proposed here. If we substitute the following parameters in the system of equations (1): γ for γ_j (all infectious stages have the same infectious period), $c\beta_l$ for $\beta\varepsilon_l$ (where c is the number of sexual partners and β_l is the transmission fraction), $\sigma \to \infty$ (there is no exposed class) and $\delta = 0$ (the individuals with AIDS do not return to the susceptible status). The additional mortality rate considered by them does not matter for the calculation of R_0. With these modifications, the R_0 is readily obtained from expression (3), as

$$R_0 = \sum_{l=1}^{k} \frac{\beta_l c \gamma^{l-1}}{(\mu + \gamma)^l},$$

Although this coincides with the threshold parameter obtained by Jacquez *et al.* (see Jacquez *et al.*, 1988, Table 2, page 137), we would like to stress two points. First, our model considered the random encounter among susceptible and infectious individuals in the transmission of virus mediated by air, while Jacquez *et al.* considered the probability (AIDS diseased individuals were excluded from the sample) of a susceptible individual encountering infectious individuals in the sexual transmission of the parasite. The second is related to the severity of the disease. Our model does not consider the disease induced mortality, while AIDS disease induces a high mortality.

A potentially applicable example of heterogeneous infectivity due to the variable amount of virus is HVB infection. This disease presents a variable infectious period, but shorter than the one showed by HIV infection. Another possible example is given by tuberculosis disease, caused by *Mycobacterium tuberculosis* infection. Its long infectious period can be modeled by considering several infectious stages. Blower *et al.* (1995) considered only two different infection status to describe *Mycobacterium tuberculosis* infection.

As a second point, note that the heterogeneous immunological responses induced by the invading micro-organism is a novel and important feature of virus transmissibility. Although the host's immunological response depends strongly on the genetic and nutritional constitution of the infected individuals, its heterogeneity has not been frequently taken into account in mathematical modeling.

By considering variable immunological responses facing an invading virus, we determined the formula for the *basic reproduction ratio* for k different infection status. The model was developed by assuming the bilinear incidence rate and, for this reason, an appropriate analysis of the λ-independent term of the characteristic equation remains valid for the stability analysis. Observe that the general formula (13) for the *basic reproduction ratio* is the sum of k different immunological responses that members of infectious individuals in a community can develop. However, we remark that this formula depends

on the product $f_i\varepsilon_i$ of the i-*th* infection individual status. Since we do not have any kind of information about the fraction of individuals (f_i) that enters in each infection status, by now we cannot conclude anything about the host's immunological response acting as the selective pressure with respect to the transmissibility of the virus (ε_i).

Finally, we conjecture that, when bilinear incidence rate modeling is applied to describe microparasite transmission, especially for directly transmitted infections, then the stability can be established by an appropriate analysis of the λ-independent term of the characteristic polynomial.

Acknowledgment

We would like to thank the anonymous referees' helpful comments. They were really useful to clarify this paper.

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