Accepted Manuscript

Journal of Biological Systems

Article Title:	Are the beginning and ending phases of epidemics characterized by the next generation matrices? - A case study of drug-sensitive and resistant tuberculosis model
Author(s):	Hyun Mo Yang
DOI:	10.1142/S0218339021500157
Received:	4 August 2020
Accepted:	5 May 2021
To be cited as:	Hyun Mo Yang, Are the beginning and ending phases of epidemics characterized by the next generation matrices? - A case study of drug-sensitive and resistant tuberculosis model, *Journal of Biological Systems*, doi: 10.1142/S0218339021500157
Link to final version:	https://doi.org/10.1142/S0218339021500157

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Are the beginning and ending phases of epidemics characterized by the next generation matrices? – A case study of drug-sensitive and resistant tuberculosis model

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Abstract

In epidemiological modelling, the basic reproduction number is usually defined as being the spectral radius of the next-generation matrix evaluated at the trivial equilibrium. The global stability of the trivial equilibrium point was determined by the left eigenvector associated with that next-generation matrix. More recently, the fraction of susceptible individuals was also obtained from the next generation matrix. The gross reproduction number and the fraction of susceptible individuals were calculated by revisiting the drug-sensitive and resistant tuberculosis model. Hence, the next-generation matrices shed light on the evolution of the dynamics: the beginning of the epidemic via the basic reproduction number and approaching the epidemic's steady-state via the susceptible individuals' asymptotic fraction.

Keywords: epidemiological modeling – stability analysis – gross reproduction number – basic reproduction number – additional reproduction number

1 Introduction

The basic reproduction number (denoted by R_0) is a threshold associated with simple epidemiological modelings formulated based on the bilinear incidence rate [1]. This number measures the intensity of epidemic spreading when one case is introduced in a completely susceptible

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population. Furthermore, the evaluation of the epidemic's equilibrium values of the model can result in the fraction of susceptible individuals (denoted by s^*) given by $s^* = 1/R_0$. In other words, the multiplicative inverse of the basic reproduction number predicts the final size of an epidemic. Hence, R_0 is the unique threshold in this class of bilinear incidence modelings. However, the basic reproduction number's analytical expression is obtained from the trivial equilibrium point's stability analysis (denoted by P^0, which describes the absence of epidemic). Hence, this analysis can provide both initial (R_0) and final (s^*) phases of an epidemic.

One of the approaches to determine the stability of the trivial equilibrium point is evaluating the spectral radius (denoted by ρ) of the corresponding next-generation matrix (represented by FV^{-1}), which is associated with the basic reproduction number [2]. For instance, in the susceptible-exposed-infectious-recovered (SEIR) model, two distinct characteristic equations corresponding to two different next-generation matrices are obtained, resulting in two spectral radii $\rho\left(FV^{-1}\right) = R_0$ and $\rho\left(FV^{-1}\right) = \sqrt{R_0}$. Another approach is the adoption of the sum of coefficients of the characteristic equation as the basic reproduction number, which was proposed in [3] and proved in [4]. According to this approach, the SEIR model presents only one threshold R_0, although two spectral radii are obtained. The validity of $s^* = 1/R_0$ is a consequence of a unique threshold from two different characteristic equations. In contrast, the SIR model has one characteristic equation corresponding to a unique next-generation matrix with the spectral radius $\rho\left(FV^{-1}\right) = R_0$, and $s^* = 1/R_0$ must be obtained from the calculation of the fraction of the susceptible individuals at the steady-state. However, in more complex models involving more than one transmission route, an additional threshold appears. In [3], two procedures were presented aiming at the calculation of these two thresholds, which were named the gross reproduction number (denoted by R_g, with $R_g = R_0 + R_a$, where R_a is the additional reproduction number) and the multiplicative inverse of the fraction of the susceptible individuals $1/s^*$. As a consequence of two different thresholds, the gross reproduction number and the fraction of susceptible individuals at equilibrium does not satisfy $s^* = 1/R_g$ (notice that $s^* = 1/R_g$, only if $R_a = 0$ resulting in $R_g = R_0$).

Therefore, the next-generation matrix can shed light on the beginning of the epidemic via the basic (or gross) reproduction number and the approaching to the epidemic's level via the susceptible individuals' asymptotic fraction. This paper aims to describe these two distinct phases of an epidemic, which is possible by constructing the next-generation matrix differently. The drug-sensitive and resistant tuberculosis transmission model is taken as a case study [5] to show that different next-generation matrices characterize the beginning (introduction of infection) and the asymptotic level (final size) of the epidemic. This model is revisited due to more elaborated procedures to calculate both thresholds. More simple SEIR and dengue encompassing transovarial transmission models are taken as further examples.

The paper is structured as follows. In section 2, a brief description of the drug-sensitive and resistant tuberculosis model is provided to calculate the gross reproduction number and the fraction of susceptible individuals by different next-generation matrix constructions. Discussion is presented in section 3, and Conclusion is given in section 4.

2 Drug-sensitive and resistant tuberculosis model – A case study

Ineffective treatment of tuberculosis leads to the emergence of multidrug-resistant (MDR) *Mycobacterium tuberculosis* to the two most potent first-line medications (isoniazid and rifampin) [6]. Tuberculosis is responsible for many deaths worldwide, and in 2017, MDR tuberculosis contributed to 14% of these deaths globally [7].

In [5], a tuberculosis transmission model was proposed, including drug treatment. They assumed that failure in treatment could arise drug-resistant *M. tuberculosis*, resulting in the model

$$\begin{cases} \frac{d}{d\tau}s &= \mu - \beta_1 i_1 s - \beta_2 i_2 s - \mu s \\ \frac{d}{d\tau}e_1 &= \beta_1 i_1 s + (1-q)\,\xi i_1 + \eta k_1 i_2 - (\mu+\gamma)\,e_1 \\ \frac{d}{d\tau}i_1 &= \gamma e_1 + p\gamma e_2 - (\mu+\alpha+\xi)\,i_1 \\ \frac{d}{d\tau}e_2 &= \beta_2 i_2 s + \eta k_2 i_2 - (\mu+\gamma)\,e_2 \\ \frac{d}{d\tau}i_2 &= (1-p)\,\gamma e_2 + q\xi i_1 - [\mu+\alpha+\eta\,(k_1+k_2)]\,i_2, \end{cases} \tag{1}$$

where the fraction of susceptible individuals is s, the fractions of exposed and infectious with drug-sensitive tuberculosis are e_1 and i_1, and the fractions of exposed and infectious with drug-resistant tuberculosis are e_2 and i_2.

Model parameters are briefly described (see [5]). The drug-sensitive and drug-resistant transmission rates are β_1 and β_2. Parameters μ and α are the natural and tuberculosis induced mortality rates, γ is the endogenous reactivation rate, ξ and η are drug-sensitive and drug-resistant treatment rates, p is the proportion of drug-resistant exposed tuberculosis individuals that develop drug-sensitive infectious individuals, q is the probability that treatment failure occurs due to the development of antibiotic resistance, and k_1 and k_2 are the relative treatment efficacy of drug-sensitive and drug-resistant patients.

In [5], the authors obtained a threshold applying **M**-matrix theory; however, neither gross reproduction number (R_g) nor the fraction of susceptible individuals (s^*) were obtained. The tuberculosis model considering drug-sensitive and resistant strains presents a certain difficulty in the computation of both thresholds.

2.1 Equilibrium points

The system of equations (1) has the trivial equilibrium P^0, or disease-free equilibrium, given by

$$P^0 = (\bar{s} = 1, \bar{e}_1 = 0, \bar{i}_1 = 0, \bar{e}_2 = 0, \bar{i}_2 = 0)\,.$$

The non-trivial equilibrium P^*, or endemic equilibrium, is given by

$$P^* = (\bar{s} = s^*, \bar{e}_1 = e_1^*(s^*), \bar{\imath}_1 = i_1^*(s^*), \bar{e}_2 = e_2^*(s^*), \bar{\imath}_2 = i_2^*(s^*)),$$

where the coordinates (they are written as a function of s^*) are

$$\begin{cases} e_1^*(s^*) &= \dfrac{[\beta_1 s^* + (1-q)\,\xi]\, i_1^*(s^*) + \eta k_1 i_2^*(s^*)}{\mu+\gamma} \\ i_1^*(s^*) &= \dfrac{\gamma e_1^*(s^*) + p\gamma e_2^*(s^*)}{\mu+\alpha+\xi} \\ e_2^*(s^*) &= \dfrac{[\beta_2 s^* + \eta k_2]\, i_2^*(s^*)}{\mu+\gamma} \\ i_2^*(s^*) &= \dfrac{\mu+\alpha+\eta-\frac{\gamma}{\mu+\gamma}\,[\beta_1 s^* + (1-q)\,\xi]}{\frac{\gamma}{\mu+\gamma}\,[\eta k_1 + p\,(\beta_2 s^* + \eta k_2)]} i_1(s^*), \end{cases} \tag{2}$$

with the fraction of susceptible individuals s^* being the positive solution of $Pol(s) = 0$, a second-degree polynomial given by

$$\begin{aligned} Pol(s) &= R_{10}R_{20}s^2 - [R_{10}\,(1-R_{21}) + R_{20}\,(1-R_{11}) + R_{31}]\, s + \\ &\quad (1-R_{11})\,(1-R_{21})\left[1 - \tfrac{R_{32}}{(1-R_{11})(1-R_{21})}\right], \end{aligned} \tag{3}$$

where the parameters R_{ij} are given by

$$\begin{cases} R_{10} = \frac{\gamma}{\mu+\gamma}\frac{\beta_1}{\mu+\alpha+\xi} & \text{and} \quad R_{11} = \frac{\gamma}{\mu+\gamma}\frac{\xi}{\mu+\alpha+\xi}\,(1-q) \\ R_{20} = \frac{\gamma}{\mu+\gamma}\,(1-p)\,\frac{\beta_2}{\mu+\alpha+\eta(k_1+k_2)} & \text{and} \quad R_{21} = \frac{\eta k_2}{\mu+\alpha+\eta(k_1+k_2)}\frac{\gamma}{\mu+\gamma}\,(1-p) \\ R_{31} = \frac{\gamma}{\mu+\gamma}p\frac{\xi}{\mu+\alpha+\xi}q\frac{\beta_2}{\mu+\alpha+\eta(k_1+k_2)} & \text{and} \quad R_{32} = \frac{\eta(k_1+pk_2)}{\mu+\alpha+\eta(k_1+k_2)}\frac{\gamma}{\mu+\gamma}\frac{\xi}{\mu+\alpha+\xi}q. \end{cases} \tag{4}$$

The second-degree polynomial $Pol(s)$ has two positive roots (see Appendix A): The small root s_s^* is given by

$$s^* \equiv s_s^* = \frac{[R_{10}\,(1-R_{21}) + R_{20}\,(1-R_{11}) + R_{31}] - \sqrt{\Delta}}{2R_{10}R_{20}}, \tag{5}$$

and the big one s_b^* is given by

$$s_b^* = \frac{[R_{10}\,(1-R_{21}) + R_{20}\,(1-R_{11}) + R_{31}] + \sqrt{\Delta}}{2R_{10}R_{20}}. \tag{6}$$

However, only one (the small solution s_s^*) has biological meaning (all coordinates of the non-trivial equilibrium point are positive). Particular solutions of the biologically feasible s_s^* are given in Appendix A. Appendix B presents the interpretations of parameters R_{ij} provided by equation (4).

2.2 Thresholds – R_g and s^*

Instead of the spectral radius of the characteristic equation, the sum of the coefficients of this equation is taken as the threshold [3] [4].

The local stability of the trivial equilibrium point P^0 is assessed by the next-generation matrix method. In the preceding section, the fraction of the susceptible individuals at endemic equilibrium s_s^* was evaluated. In this section, this value will be obtained from the next-generation matrix evaluated at the trivial equilibrium point. Briefly, the next-generation matrix is constructed based on the transmission (f) and transition (v) vectors, from which matrices F and V evaluated at the trivial equilibrium are obtained, resulting in the next-generation matrix FV^{-1} [2]. The vectors f and v are obtained eliminating the susceptible individuals' equation in (1), that is, a subsystem considering variables $x = (e_1, i_1, e_2, i_2)^T$, where superscript T stands for the transposition of a matrix.

In the drug-sensitive and resistant tuberculosis transmissions model, there are many combinations to construct the vectors f and v, resulting in different next-generation matrices. The gross reproduction number (R_g) is obtained in all combinations of bilinear incidence terms ($\beta_1 i_1 s$ and $\beta_2 i_2 s$) associated with transition terms (γe_1 and $p\gamma e_2$, for instance) to construct f and v, except only one construction which yields the fraction of susceptible individuals (s^*) [3] [8]. Here, only two next-generation matrices evaluated at the trivial equilibrium P^0 are shown.

2.2.1 The gross reproduction number R_g

To obtain the gross reproduction number, the simplest diagonal matrix V is considered. Hence, the vectors f and v are

$$f = \begin{pmatrix} \beta_1 i_1 s + (1-q)\,\xi i_1 + \eta k_1 i_2 \\ \gamma e_1 + p\gamma e_2 \\ \beta_2 i_2 s + \eta k_2 i_2 \\ (1-p)\,\gamma e_2 + q\xi i_1 \end{pmatrix} \quad \text{and} \quad v = \begin{pmatrix} (\mu+\gamma)\,e_1 \\ (\mu+\alpha+\xi)\,i_1 \\ (\mu+\gamma)\,e_2 \\ [\mu+\alpha+\eta\,(k_1+k_2)]\,i_2 \end{pmatrix}$$

from which the matrices F and V are obtained as

$$F = \begin{bmatrix} 0 & \beta_1 + (1-q)\,\xi & 0 & \eta k_1 \\ \gamma & 0 & p\gamma & 0 \\ 0 & 0 & 0 & \beta_2 + \eta k_2 \\ 0 & q\xi & (1-p)\,\gamma & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \mu+\gamma & 0 & 0 & 0 \\ 0 & \mu+\alpha+\xi & 0 & 0 \\ 0 & 0 & \mu+\gamma & 0 \\ 0 & 0 & 0 & \varphi \end{bmatrix},$$

with $\varphi = \mu + \alpha + \eta\,(k_1 + k_2)$. The next-generation matrix FV^{-1} is

$$FV^{-1} = \begin{bmatrix} 0 & \dfrac{\beta_1 + (1-q)\,\xi}{\mu+\alpha+\xi} & 0 & \dfrac{\eta k_1}{\mu+\alpha+\eta\,(k_1+k_2)} \\ \dfrac{\gamma}{\mu+\gamma} & 0 & \dfrac{p\gamma}{\mu+\gamma} & 0 \\ 0 & 0 & 0 & \dfrac{\beta_2+\eta k_2}{\mu+\alpha+\eta\,(k_1+k_2)} \\ 0 & \dfrac{q\xi}{\mu+\alpha+\xi} & \dfrac{(1-p)\,\gamma}{\mu+\gamma} & 0 \end{bmatrix},$$

and the characteristic equation corresponding to FV^{-1} is

$$\left(\lambda^2 - R_1\right)\left(\lambda^2 - R_2\right) - R_3\lambda = 0, \tag{7}$$

where R_i, with $i = 1$, 2 and 3, are given by

$$\begin{cases} R_1 &= R_{10} + R_{11} \\ R_2 &= R_{20} + R_{21} \\ R_3 &= R_{31} + R_{32}, \end{cases} \tag{8}$$

with R_{ij} being given by equation (4). According to [3], the gross reproduction number R_g is given by

$$R_g = \max\left\{R_1, R_2, \frac{R_3}{(1-R_1)\,(1-R_2)}\right\}, \tag{9}$$

where max stands for the maximum value among them. Notice that the spectral radius $\rho\,(FV^{-1})$ can not be obtained analytically.

The condition for the trivial equilibrium point P^0 to be locally asymptotically stable (LAS) is $R_g < 1$. If $R_g > 1$, P^0 is unstable, and the unique non-trivial equilibrium point P^* appears. Therefore, R_g is a threshold parameter.

Let two special cases be considered for R_g. Firstly, consider $R_{32} = 0$, that is, there is no failure in treatment or $R_{31} = 0$, that is, there is no passage from i_1 to i_2. In this case, R_g is

$$R_g = \max\left\{R_1, R_2, \tfrac{R_{31}}{(1-R_1)(1-R_2)}\right\} \quad \text{or} \quad R_g = \max\left\{R_1, R_2, \tfrac{R_{32}}{(1-R_1)(1-R_2)}\right\},$$

showing that drug-sensitive and drug-resistant strains of tuberculosis can reach an endemic level even when $R_1 < 1$ and $R_2 < 1$, but if $R_{31}/\left[(1-R_1)\,(1-R_2)\right] > 1$ or $R_{32}/\left[(1-R_1)\,(1-R_2)\right] > 1$ is satisfied. The joint propagation of drug-sensitive and drug-resistant strains facilitates the persistence of the epidemic.

However, if $R_{32} = 0$ and $R_{31} = 0$, R_g is

$$R_g = \max\left\{R_1, R_2\right\},$$

and both strains propagate independently. Notice that if $R_1 > 1$ and $R_2 < 1$, drug-sensitive tuberculosis is at the endemic level, but drug-resistant tuberculosis goes to extinction, and vice-versa if $R_1 < 1$ and $R_2 > 1$. Additionally, if $R_{11} = 0$ and $R_{21} = 0$, the basic reproduction number R_0 is

$$R_0 = \max\left\{R_{10}, R_{20}\right\}. \tag{10}$$

Hence, the additional reproduction number (R_{11} or R_{21}) is why name R_g as the gross reproduction number.

Let a different choice of vectors f and v be exemplified. If the vectors f and v are

$$f = \begin{pmatrix} \beta_1 i_1 s + (1-q)\,\xi i_1 \\ \gamma e_1 + p\gamma e_2 \\ \beta_2 i_2 s + \eta k_2 i_2 \\ (1-p)\,\gamma e_2 + q\xi i_1 \end{pmatrix} \quad \text{and} \quad v = \begin{pmatrix} -\eta k_1 i_2 + (\mu+\gamma)\,e_1 \\ (\mu+\alpha+\xi)\,i_1 \\ (\mu+\gamma)\,e_2 \\ \left[\mu+\alpha+\eta\,(k_1+k_2)\right] i_2 \end{pmatrix},$$

the matrices F and V are

$$F = \begin{bmatrix} 0 & \beta_1 + (1-q)\,\xi & 0 & 0 \\ \gamma & 0 & p\gamma & 0 \\ 0 & 0 & 0 & \beta_2 + \eta k_2 \\ 0 & q\xi & (1-p)\,\gamma & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} \mu+\gamma & 0 & 0 & -\eta k_1 \\ 0 & \mu+\alpha+\xi & 0 & 0 \\ 0 & 0 & \mu+\gamma & 0 \\ 0 & 0 & 0 & \varphi \end{bmatrix},$$

with $\varphi = \mu + \alpha + \eta\,(k_1 + k_2)$. The next-generation matrix FV^{-1} is

$$FV^{-1} = \begin{bmatrix} 0 & \dfrac{\beta_1 + (1-q)\,\xi}{\mu+\alpha+\xi} & 0 & 0 \\ \dfrac{\gamma}{\mu+\gamma} & 0 & \dfrac{p\gamma}{\mu+\gamma} & \dfrac{\gamma}{\mu+\gamma}\dfrac{\eta k_1}{\mu+\alpha+\eta\,(k_1+k_2)} \\ 0 & 0 & 0 & \dfrac{\beta_2+\eta k_2}{\mu+\alpha+\eta\,(k_1+k_2)} \\ 0 & \dfrac{q\xi}{\mu+\alpha+\xi} & \dfrac{(1-p)\,\gamma}{\mu+\gamma} & 0 \end{bmatrix},$$

and the characteristic equation corresponding to FV^{-1} is

$$\left(\lambda^2 - R_1\right)\left(\lambda^2 - R_2\right) - \left[R_{32}^2\lambda^2 + \left(R_{31} + R_{32}^1\right)\lambda\right] = 0,$$

where

$$R_{32}^1 = \frac{\eta k_1}{\mu+\alpha+\eta(k_1+k_2)}\frac{\gamma}{\mu+\gamma}\frac{\xi}{\mu+\alpha+\xi}q \quad \text{and} \quad R_{32}^2 = \frac{\eta p k_2}{\mu+\alpha+\eta(k_1+k_2)}\frac{\gamma}{\mu+\gamma}\frac{\xi}{\mu+\alpha+\xi}q,$$

with $R_{32} = R_{32}^1 + R_{32}^2$. The sum of the coefficients of $R_{32}^2\lambda^2 + \left(R_{31} + R_{32}^1\right)\lambda$ is exactly R_3, and the gross reproduction number is given by equation (9).

2.2.2 The fraction of susceptible individuals s^*

There is a unique way to obtain the fraction of susceptible individuals – The infection matrix F must be the most straightforward (matrix with the least number of non-zeros). In other words, the vector f must carry only the bilinear incidence terms. Hence, the vectors f and v are

$$f = \begin{pmatrix} \beta_1 i_1 s \\ 0 \\ \beta_2 i_2 s \\ 0 \end{pmatrix} \quad \text{and} \quad v = \begin{pmatrix} -(1-q)\,\xi i_1 - \eta k_1 i_2 + (\mu+\gamma)\,e_1 \\ -\gamma e_1 - p\gamma e_2 + (\mu+\alpha+\xi)\,i_1 \\ -\eta k_2 i_2 + (\mu+\gamma)\,e_2 \\ -(1-p)\,\gamma e_2 - q\xi i_1 + [\mu+\alpha+\eta\,(k_1+k_2)]\,i_2 \end{pmatrix}$$

from which the matrices F and V are obtained as

$$F = \begin{bmatrix} 0 & \beta_1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta_2 \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \mu+\gamma & -(1-q)\,\xi & 0 & -\eta k_1 \\ -\gamma & \mu+\alpha+\xi & -p\gamma & 0 \\ 0 & 0 & \mu+\gamma & -\eta k_2 \\ 0 & -q\xi & -(1-p)\,\gamma & \mu+\alpha+\eta\,(k_1+k_2) \end{bmatrix}.$$

The next-generation matrix FV^{-1} is

$$FV^{-1} = \begin{bmatrix} \beta_1 n_{11} & \beta_1 n_{12} & \beta_1 n_{13} & \beta_1 n_{14} \\ 0 & 0 & 0 & 0 \\ \beta_2 n_{31} & \beta_2 n_{32} & \beta_2 n_{33} & \beta_2 n_{34} \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

(n_{ij} are omitted) and the characteristic equation corresponding to FV^{-1} is

$$\lambda^2 \left[(\lambda - \beta_1 n_{11})\,(\lambda - \beta_2 n_{33}) - \beta_1 n_{13} \beta_2 n_{31} \right] = 0,$$

or, letting $\chi_1 = \beta_1 n_{11}$, $\chi_2 = \beta_2 n_{33}$, $\chi_3 = \beta_1 n_{13}$, and $\chi_4 = \beta_2 n_{31}$,

$$\lambda^2 \left[(\lambda - \chi_1)\,(\lambda - \chi_2) - \chi_3 \chi_4 \right] = 0, \tag{11}$$

where χ_i are given by ($p \neq 0$)

$$\begin{cases} \chi_1 &= \dfrac{R_{10}}{1-R_{11}} \left[1 - \dfrac{R_{32}}{(1-R_{11})\,(1-R_{21})} \right]^{-1} \\ \chi_2 &= \dfrac{R_{20}\,(1-R_{11}) + R_{31}}{(1-R_{11})\,(1-R_{21})} \left[1 - \dfrac{R_{32}}{(1-R_{11})\,(1-R_{21})} \right]^{-1} \\ \chi_3 &= p \dfrac{R_{10}}{1-R_{11}} \dfrac{1 + \frac{1}{p} R_{33}}{1-R_{21}} \left[1 - \dfrac{R_{32}}{(1-R_{11})\,(1-R_{21})} \right]^{-1} \\ \chi_4 &= \dfrac{1}{p} \dfrac{R_{20}\,(1-R_{11}) + R_{31}}{(1-R_{11})\,(1-R_{21})} \left[1 - \dfrac{R_{32}}{(1-R_{11})\,(1-R_{21})} \right]^{-1}, \end{cases}$$

with R_{ij} being given by equation (4), and the additional R_{33} being given by

$$R_{33} = \frac{\eta k_1}{\mu + \alpha + \eta\,(k_1 + k_2)} \frac{\gamma}{\mu + \gamma}\,(1 - p)\,.$$

Notice that the parameter R_{33} does not appear in the calculation of the fraction of susceptible individuals s_s^* nor in the gross reproduction number R_g.

The characteristic equation (11) has two equal eigenvalues $\lambda = 0$, and the other two are given by solutions of

$$\lambda^2 - (\chi_1 + \chi_2)\,\lambda + \chi_1\chi_2 - \chi_3\chi_4 = 0, \tag{12}$$

which has two positive eigenvalues. (It is easy to show that $\chi_1\chi_2 - \chi_3\chi_4 > 0$ and $(\chi_1 + \chi_2)^2 - 4\,(\chi_1\chi_2 - \chi_3\chi_4) > 0$.) Hence, the spectral radius $\rho\,(FV^{-1})$ is the big solution, that is,

$$\rho\left(FV^{-1}\right) = \frac{(\chi_1 + \chi_2) + \sqrt{(\chi_1 + \chi_2)^2 - 4\,(\chi_1\chi_2 - \chi_3\chi_4)}}{2}. \tag{13}$$

The trivial equilibrium point P^0 is LAS if $\rho\,(FV^{-1}) < 1$, and unstable if $\rho\,(FV^{-1}) > 1$, and the unique non-trivial equilibrium point P^* appears. Hence, P^* is biologically feasible if $\rho\,(FV^{-1}) > 1$, that is, $s_s^* < 1$, and $\rho\,(FV^{-1}) = 1/s_s^*$ is another threshold parameter.

It is clear that this new threshold parameter $\rho\,(FV^{-1})$, given by equation (13), can not be associated with the gross reproduction number R_g, given by equation (9), through $\rho^{-1}\,(FV^{-1}) = 1/R_g$. To clarify a second threshold parameter's appearance, let two particular cases of $\rho\,(FV^{-1})$ be considered.

Firstly, when $\beta_2 = 0$ ($\chi_2 = \chi_4 = 0$), the spectral radius of equation (11) is $\rho_1\,(FV^{-1})$, and equation (13) becomes

$$\rho_1^{-1}\left(FV^{-1}\right) = \frac{1 - R_{11}}{R_{10}}\left[1 - \frac{R_{32}}{(1 - R_{11})\,(1 - R_{21})}\right]. \tag{14}$$

Comparing $\rho_1\,(FV^{-1})$ with equation (A.1) in Appendix A, it is clear that $\rho_1\,(FV^{-1}) = 1/s_s^*$. When $\beta_1 = 0$ ($\chi_1 = \chi_3 = 0$), the spectral radius of equation (11) is $\rho_2\,(FV^{-1})$, and equation (13) becomes

$$\rho_2^{-1}\left(FV^{-1}\right) = \frac{(1 - R_{11})\,(1 - R_{21})}{R_{20}\,(1 - R_{11}) + R_{31}}\left[1 - \frac{R_{32}}{(1 - R_{11})\,(1 - R_{21})}\right]. \tag{15}$$

Comparing $\rho_2\,(FV^{-1})$ with equation (A.3) in Appendix A, it is clear that $\rho_2\,(FV^{-1}) = 1/s_s^*$.

Secondly, letting $R_{32} = 0$ besides $\beta_2 = 0$, the spectral radius (14) becomes

$$\rho_1^{-1}\left(FV^{-1}\right) = \frac{1 - R_{11}}{R_{10}}, \tag{16}$$

which is equal to the fraction of susceptible individuals given by equation (A.2) in Appendix A. For this reason, R_{10} is the basic reproduction number of drug-sensitive strain, and R_{11} is

the additional reproduction number. Now, letting $R_{32} = 0$ and $R_{31} = 0$ besides $\beta_1 = 0$, the spectral radius (15) becomes

$$\rho_2^{-1}\left(FV^{-1}\right) = \frac{1 - R_{21}}{R_{20}},$$

which is equal to the fraction of susceptible individuals given by equation (A.4) in Appendix A, and R_{20} is the basic reproduction number of drug-resistant strain, and R_{21} is the additional reproduction number. Notice that when the additional reproduction numbers $R_{11} = 0$ and $R_{21} = 0$, then $s^* = 1/R_0$, where R_0 is given by equation (10), having a unique threshold.

When $\beta_1 > 0$ and $\beta_2 > 0$, it is not an easy task to prove that $\rho\left(FV^{-1}\right) = 1/s_s^*$, where $\rho\left(FV^{-1}\right)$ and s^* are given by equations (13) and (5). The main reason is the parameter R_{33} appearing in $\rho\left(FV^{-1}\right)$ but not in s^*, but numerically $\rho\left(FV^{-1}\right) = 1/s_s^*$ can be verified (see below). Hence, the spectral radius is exactly the multiplicative inverse of the fraction of susceptible individuals.

3 Discussion

Drug-sensitive and resistant *M. tuberculosis* transmission model was taken as an example of the next-generation matrix's application to describe both the beginning and ending phases of the epidemic. Depending on the construction of vectors f and v, two thresholds were obtained from the characteristic equations corresponding to the next-generation matrix FV^{-1}. Traditionally, the spectral radius was taken as the basic reproduction number [9] [10]. However, a different approach was proposed in [3], consisting of summing the characteristic equation's coefficients instead of evaluating the spectral radius. This approach has a substantial advantage: A recipe to construct vectors f and v is not necessary [11].

However, depending on the model's complexity, the sum of the coefficients is insufficient to determine the gross reproduction number. The model of tuberculosis dealt with here is an example. The method used to obtain two thresholds R_g and $\rho\left(FV^{-1}\right) = 1/s^*$ is summarized: Let the characteristic equation corresponding to next-generation matrix FV^{-1} be written as

$$\Lambda(\lambda) = \Lambda_n(\lambda)\Lambda_m(\lambda) - \Lambda_p(\lambda), \tag{17}$$

where $\Lambda_n(\lambda) = \Lambda_n(\lambda) = \lambda^n - a_{n-1}\lambda^{n-1} - \cdots - a_1\lambda - a_0$, $\Lambda_m(\lambda) = \lambda^m - b_{m-1}\lambda^{m-1} - \cdots - b_1\lambda - b_0$, and $\Lambda_p(\lambda) = c_p\lambda^p + \cdots + c_1\lambda + c_0$, with $\Omega_n = \sum_{i=0}^{n-1} a_i$, $\Omega_m = \sum_{i=0}^{m-1} b_i$ and $\Omega_p = \sum_{i=0}^{p} c_i$ (all coefficients are non-negative).

(A) If vector f carries only bilinear terms regarding infection, and all terms are left to vector v (the number of non-zero elements is the least in the matrix F and the most in the matrix V), then the spectral radius $\rho\left(FV^{-1}\right)$ of the characteristic equation $\Lambda(\lambda) = 0$ is the multiplicative inverse of the fraction of susceptible individuals s^*, that is, $\rho\left(FV^{-1}\right) = 1/s^*$.

(B) In all constructions of vectors f and v except case (A), the sum of the coefficients of each equation $\Lambda_n(\lambda)$, $\Lambda_m(\lambda)$ and $\Lambda_p(\lambda)$ forming the characteristic equation $\Lambda(\lambda)$ corresponding to the next-generation matrix FV^{-1} enters in the calculation of the gross reproduction number R_g, that is,

$$R_g = \max\left\{\Omega_n, \Omega_m, \frac{\Omega_p}{(1-\Omega_n)(1-\Omega_m)}\right\}, \tag{18}$$

where max stands for the maximum value among Ω_n, Ω_m and $\Omega_p/\left[(1-\Omega_n)(1-\Omega_m)\right]$. Hence, the best choice to calculate R_g is the construction of vectors f and v such that the matrix V is diagonal.

Observe that equation (17) has at least two positive solutions (excluding the possibility of the absence of a positive solution). For this reason, the threshold in (A) must be the spectral radius. However, suppose there are no interactions between pathogens or strains, that is, $\Lambda_p(\lambda) = 0$. In this case, there is a unique positive solution for each equation $\Lambda_n(\lambda) = 0$ and $\Lambda_m(\lambda) = 0$, from which $s^* = 1/\Omega_n$ or $s^* = 1/\Omega_m$ (instead of calculating the spectral radius). In the absence of the additional reproduction number, that is, $R_g = R_0$, resulting in $s^* = 1/R_g$. This is called a simplified version of (A).

The cases (A) and (B) were cited in [3], but only (B) was briefly exemplified. Here, more details regarding the application of (B) in tuberculosis modeling encompassing drug-sensitive and drug-resistant strains were presented. The fraction of susceptible individuals in (A) deserves some comments. The steady-state fraction of the susceptible individuals was obtained from the roots of the second-degree polynomial (5), which has two positive solutions. It was shown that only the small one has biological meaning (the big solution generates negative coordinates for the non-trivial equilibrium). The stability of the trivial equilibrium point was assessed also by the roots of the second-degree polynomial, given by the characteristic equation (12), presenting two positive solutions. Hence, two reasons are behind the relationship between the spectral radius and the fraction of susceptible individuals.

1. When a characteristic equation has more than one positive eigenvalue, the spectral radius $\rho\left(FV^{-1}\right)$ must be chosen as the threshold.

2. The trivial equilibrium is LAS if the spectral radius is lower than one ($\rho\left(FV^{-1}\right) < 1$) and unstable otherwise. Hence, the epidemic is settled at the community if $\rho\left(FV^{-1}\right) > 1$, that is, $s^* < 1$.

Hence, at the endemic level, the spectral radius guarantees value higher than one, and, consequently, its inverse is lower than one. In particular cases, the relationship $\rho\left(FV^{-1}\right) = 1/s_s^*$ was demonstrated analytically. However, as pointed out, it is not an easy task to showing analytically that the small solution of equation (3) is equal to the inverse of the spectral radius of the characteristic equation (12), $s_s^* = 1/\rho\left(FV^{-1}\right)$, but it can be verified numerically.

For instance, letting $\mu = 0.0154$, $\alpha = 0.33$, $\gamma = 0.025$, $\xi = 0.1$, $\eta = 0.5$, $\beta_1 = 4,55$ and $\beta_2 = 6.25$ (all in $years^{-1}$); and $p = 0.05$, $q = 0.4$, $k_1 = 0.87$ and $k_2 = 0.53$ (dimensionless), the reproduction numbers are, from equation (8), $R_1 = 6.4$, $R_2 = 3.7$ and $R_3 = 0.04$, and $R_{in} = 0.003$, where $R_{in} = R_{32}/\left[\left(1 - R_1\right)\left(1 - R_2\right)\right]$. Hence, the gross reproduction number is $R_g = R_1 = 6.4$ according to equation (9), particular application of equation (18). The small and large fraction of susceptible individuals are, from (5) and (6), $s_s^* = 0.1341$ and $s_g^* = 0.2537$. From equation (13), the inverse of the spectral radius is $1/\rho\left(FV^{-1}\right) = 0.1314$, while the inverse of the small eigenvalue of equation (12) is 0.2537. Hence, the inverse of the spectral radius is equal to the small fraction of susceptible individuals, which is in accordance with the asymptotic value obtained by Runge-Kutta method.

It is worth stressing the fact that the characteristic equations (7) and (11) have similar structure. However, the gross reproduction number is given by equation (9), while the inverse of the fraction of susceptible individuals is given by the spectral radius of equation (12).

The particular case $\beta_2 = 0$ and $R_{32} = 0$ considered in the previous section is quite similar to that model considered by Driessche and Watmough [9]. In their analysis, they did not account for the existence of two thresholds; for this reason, they considered that the basic reproduction number is given by equation (16), not by equation (8).

The calculations of one or two thresholds are exemplified considering two simple models. In the SEIR and dengue with the transovarial transmission models, there is only one pathogen, hence $\Lambda_p(\lambda) = 0$ and $\Lambda_m(\lambda) = 1$ in equation (17), resulting in $\Lambda(\lambda) = \Lambda_n(\lambda)$, with $\Omega = \Omega_n = \sum_{i=0}^{n-1} a_i$, and $\Lambda(\lambda) = 0$ has only one positive solution. Instead of the spectral radius of $\Lambda(\lambda) = 0$, the sum of the coefficients Ω of $\Lambda(\lambda)$ is taken as the threshold.

Let the well-known SEIR model be considered (see, for instance, [1]). The model describes a pathogen being transmitted directly from infectious to susceptible individuals, which is given by

$$\begin{cases} \dfrac{d}{dt}s &= \mu - \beta si - \mu s \\ \dfrac{d}{dt}e &= \beta si - (\mu + \gamma)\, e \\ \dfrac{d}{dt}i &= \gamma e - (\mu + \sigma)\, i \\ \dfrac{d}{dt}r &= \sigma i - \mu r, \end{cases} \tag{19}$$

where s, e, i and r are the fractions of, respectively, susceptible, exposed, infectious and recovered individuals. The model parameters are the mortality rate μ, the contact rate β, the infectious γ and recovery σ rates.

The system of equations (19) has two equilibrium points: the trivial $P^0 = (1, 0, 0, 0)$ and the non-trivial $P^* = (s^*, e^*, i^*, r^*)$, where the fraction of susceptible individuals is $s^* = 1/R_0$, with the basic reproduction number R_0 being given by

$$R_0 = \frac{\gamma}{\mu + \gamma} \times \frac{\beta}{\mu + \sigma}. \tag{20}$$

The next-generation matrix is obtained considering the vector of variables $x = (e, i)^T$. In this model, there are only two next-generation matrices evaluated at the trivial equilibrium P^0.

The basic reproduction number R_0 is obtained according to (B), that is, the vectors are $f = (\beta i s, \gamma e)^T$ and $v = ((\mu + \gamma)\, e, (\mu + \sigma)\, i)^T$. The characteristic equation corresponding to the next-generation matrix obtained from the diagonal matrix V is

$$\lambda^2 - R_0 = 0, \tag{21}$$

where the basic reproduction number R_0 is given by equation (20).

Let the procedure stated in the simplified version of (A) be applied to obtain the fraction of susceptible individuals s^*. In this case, the vectors are $f = (\beta i s, 0)^T$ and $v = ((\mu + \gamma)\, e, -\gamma e + (\mu + \sigma)\, i)^T$. The characteristic equation corresponding to the next-generation matrix obtained from the non-diagonal matrix V is

$$\lambda^2 - R_0 \lambda = 0, \tag{22}$$

where R_0 is given by equation (20). According to the simplified version of (A), this full matrix V must originate the second threshold $1/s^*$ as the sum of coefficients. However, the sum (in this case, the spectral radius) is equal to that obtained in equation (21). Hence, the inverse of R_0 is the fraction of susceptible individuals, that is, $s^* = 1/R_0$, which is one of the coordinates of P^*.

Notice that in the SEIR model, the spectral radius $\rho\left(FV^{-1}\right)$ of equation (21) is $\rho\left(FV^{-1}\right) = \sqrt{R_0}$, while the spectral radius of equation (22) is $\rho\left(FV^{-1}\right) = R_0$. For this reason, some authors claim that the construction of vectors f and v according to the simplified version of (A) is correct [9]. However, the sum of the coefficients of equations (21) and (22) is the same, establishing that there is a unique threshold, hence $R_0 = \rho\left(FV^{-1}\right) = 1/s^*$. Notice that the non-trivial equilibrium point P^* has one of the coordinates $s^* = 1/R_0$. However, in the SIR model, there is only one characteristic equation (the next-generation matrix is a unitary matrix), and the spectral radius is indeed the basic reproduction number, and there is not a second threshold. For this reason, the fraction of susceptible individuals being the inverse of the basic reproduction number can be obtained only from the equilibrium value of s^*.

Let a dengue encompassing the transovarial transmission model [8] be considered. In the SEIR model, there is one pathogen, one population, and one route of transmission. In contrast, there are two populations in dengue with the transovarial transmission model, one common pathogen, but two transmission routes.

The model presented in [8] considered both horizontal and transovarial transmission routes

transmitting the dengue virus. The system of differential equations describing this model is

$$\begin{cases} \frac{d}{dt}l_1 &= qf\phi\left[m_1+(1-\alpha)\,m_2\right]\left(1-\frac{l_1+l_2}{C}\right)-(\sigma_a+\mu_a)\,l_1 \\ \frac{d}{dt}l_2 &= qf\phi\alpha m_2\left(1-\frac{l_1+l_2}{C}\right)-(\sigma_a+\mu_a)\,l_2 \\ \frac{d}{dt}m_1 &= \sigma_a l_1-(\beta_m\phi i+\mu_f)\,m_1 \\ \frac{d}{dt}m_2 &= \sigma_a l_2+\beta_m\phi i m_1-\mu_f m_2 \\ \frac{d}{dt}s &= \mu_h-\left(\frac{\beta_h\phi}{N}m_2+\mu_h\right)s \\ \frac{d}{dt}i &= \frac{\beta_h\phi}{N}m_2 s-(\sigma_h+\mu_h)\,i, \end{cases} \tag{23}$$

where the decoupled fraction of immune humans is given by $r = 1-s-i$, s and i are the fractions of susceptible and infectious humans, and N is the constant total number of the humans. The susceptible and infectious female adult mosquitoes are m_1 and m_2, with $m = m_1 + m_2$, and l_1 and l_2 represent the uninfected and infected immatures, with $l = l_1 + l_2$.

Concerning the model parameters, α is the proportion of transovarial transmission, μ_h is the birth and mortality rates of humans, and σ_h is the recovery rate. The per-capita oviposition rate is ϕ, q and f are the fractions of eggs that are hatching to larva, and that will yield female mosquitoes, respectively, C is the carrying capacity of the breeding sites, σ_a is the rate at which larva become adults, and μ_a and μ_f are the mortality rates of, respectively, immatures and adults. Finally, β_h is the transmission coefficient from mosquito to human, and β_m is the transmission coefficient from human to mosquito.

The system of equations (23) has two equilibrium points, assuming that $Q_0 > 1$, where $Q_0 = \sigma_a q f \phi / \left[(\sigma_a+\mu_a)\,\mu_f\right]$ is the basic offspring number. The trivial equilibrium P^0, or disease-free equilibrium, is given by

$$P^0 = \left(\bar{l}_1 = l^* = C\left(1-\frac{1}{Q_0}\right), \bar{l}_2 = 0, \bar{m}_1 = m^* = \frac{\sigma_a}{\mu_f}C\left(1-\frac{1}{Q_0}\right), \bar{m}_2 = 0, \bar{s} = 1, \bar{\imath} = 0\right), \tag{24}$$

and the non-trivial equilibrium P^*, or endemic equilibrium, is given by

$$P^* = \left(\bar{l}_1 = l_1^*, \bar{l}_2 = l_2^*, \bar{m}_1 = m_1^*, \bar{m}_2 = m_2^*, \bar{s} = s^*, \bar{\imath} = i^*\right),$$

where the product of the fractions of susceptible humans s^* and mosquitoes m_1^*/m^* is

$$s^* \times \frac{m_1^*}{m^*} = \frac{1-R_a}{R_0} = \frac{1}{R_0} - \frac{\alpha}{R_0}. \tag{25}$$

(see [8] for detailed calculations.) The gross reproduction number R_g is defined by

$$R_g = R_0 + R_a, \tag{26}$$

which is the sum of the basic reproduction number $R_0 = R_0^h R_0^m$ due to the horizontal transmission with the partial contributions $R_0^h = \beta_h \phi / \mu_f$ and $R_0^m = \beta_m \phi m^* / \left[(\sigma_h + \mu_h) N \right]$, and the additional reproduction number $R_a = \alpha$ due to the transovarial transmission.

Only two next-generation matrices evaluated at the trivial equilibrium P^0 are presented, with the matrices being obtained from the vector of variables $x = (m_2, i, l_2)^T$, where superscript T stands for the transposition of a matrix. (See [8] for other constructions of the vectors f and v.)

To obtain the gross reproduction number, diagonal matrix V is considered, according to (B). In this case, the vectors f and v are

$$f = \begin{bmatrix} \beta_m \phi i m_1 + \sigma_a l_2 \\ \frac{\beta_h \phi}{N} m_2 s \\ q f \phi \alpha m_2 \left(1 - \frac{l_1 + l_2}{C}\right) \end{bmatrix} \quad \text{and} \quad v = \begin{bmatrix} \mu_f m_2 \\ (\sigma_h + \mu_h)\, i \\ (\sigma_a + \mu_a)\, l_2 \end{bmatrix},$$

and the next-generation matrix FV^{-1} is

$$FV^{-1} = \begin{bmatrix} 0 & N R_0^m & \frac{\sigma_a}{\sigma_a + \mu_a} \\ \frac{1}{N} R_0^h & 0 & 0 \\ \alpha \frac{\sigma_a + \mu_a}{\sigma_a} & 0 & 0 \end{bmatrix},$$

and the corresponding characteristic equation is

$$\lambda^3 - R_g \lambda = 0, \tag{27}$$

with R_g being given by equation (26), which is the gross reproduction number (the sum of the coefficients of the characteristic equation). In the transovarial dengue transmission model, other next-generation matrices are resulting in the same gross reproduction number (see [8]).

To obtain the fraction of susceptible individuals, infection matrix F must be the most straightforward (matrix with the least number of non-zeros); thus, matrix V is the most full with non-zero elements. In this case, the vectors f and v are

$$f = \begin{bmatrix} \beta_m \phi i m_1 \\ \frac{\beta_h \phi}{N} m_2 s \\ 0 \end{bmatrix} \quad \text{and} \quad v = \begin{bmatrix} -\sigma_a l_2 + \mu_f m_2 \\ (\sigma_h + \mu_h)\, i \\ -q f \phi \alpha m_2 \left(1 - \frac{l_1 + l_2}{C}\right) + (\sigma_a + \mu_a)\, l_2 \end{bmatrix},$$

and the next-generation matrix FV^{-1} is

$$FV^{-1} = \begin{bmatrix} 0 & N R_0^m & 0 \\ \frac{1}{1-\alpha} \frac{1}{N} R_0^h & 0 & \frac{1}{1-\alpha} \frac{\sigma_a}{\sigma_a + \mu_a} \frac{1}{N} R_0^h \\ 0 & 0 & 0 \end{bmatrix}.$$

and the characteristic equation corresponding to FV^{-1} is

$$\lambda^3 - \frac{R_0}{1 - R_a} \lambda = 0. \tag{28}$$

According to the simplified version of (A), the sum of the coefficients is a threshold, that is, $1/\Omega = (1 - R_a)/R_0$. Comparing, however, with equation (25), the product of the fractions of susceptible humans and mosquitoes is indeed the threshold, that is, $s^* \times m_1^*/m^* = (1 - R_a)/R_0$. This threshold must be the product of susceptible populations since two populations are involved in the transmission.

Comparing equations (22) and (22) in the SEIR model, the relationship $s^* = 1/R_0$ is obeyed, while, from equations (27) and (28), the product $s^* \times m_1^*/m^*$ is not the inverse of R_g. Hence, two routes of transmission resulted in two different thresholds. However, if only one route of transmission is considered, letting $\alpha = 0$, then $s^* \times m_1^*/m^* = 1/R_0$, implying that there is a unique threshold R_0.

4 Conclusion

The basic reproduction number has a well-accepted interpretation: The secondary cases produced by one infectious individual when introduced in a completely susceptible population. This concept portrays the beginning of an epidemic. Nevertheless, suppose the next-generation matrix provides the initial strength of an epidemics. In this case, it is expected that it may also predict an epidemic's final size, which is indeed measured by the remaining fraction of susceptible individuals. This fraction portrays the ending phase of an epidemic, that is, those individuals who have not been infected at the steady-state. For instance, if there is only one threshold, the basic reproduction number R_0 and the final size of epidemics s^* obey $s^* = 1/R_0$. In other words, how intense is an epidemic (higher R_0), more individuals are infected, and a low number of individuals are left uninfected; hence the fraction of susceptible individuals is low ($1/R_0$).

The procedures presented in [3] can be easily applied when the characteristic equation corresponding to the next-generation matrix is given by equation (17), with $\Lambda_p(\lambda) = 0$. In this case, the sum of the coefficients of this equation is the basic (or gross) reproduction number or the fraction of susceptible individuals, as SEIR and dengue with transovarial models showed. However, when the characteristic equation corresponding to the next-generation matrix is given by equation (17), then the gross reproduction number is given by equation (18), and the spectral radius is the inverse of the fraction of susceptible individuals. This case was shown revisiting the drug-sensitive and resistant tuberculosis transmission model.

It is worth stressing that the sum of the coefficients in the characteristic equation of the next-generation matrix provides the fraction of the susceptible individuals because this equation has a unique positive eigenvalue. However, when there is not a unique positive eigenvalue, it is natural to choose the spectral radius for two reasons: (1) it is the greatest value higher than one to maintain epidemic, and, consequently, (2) the multiplicative inverse of this number is the lowest and small than one. (The fraction of susceptible individuals must be consistently lower than one.)

It is well-accepted that the basic (or gross) reproduction number obtained from the next-

generation matrix is linked to the initial phase of an epidemic. The global stability of the trivial equilibrium point can be determined by the left eigenvector associated with this next-generation matrix [10]. Besides these two significant results, the next-generation matrix can predict an epidemic's final size by allowing the calculation of the fraction of susceptible individuals at the steady-state. Therefore, depending on how the next-generation matrix is constructed, both the initial and final phases of an epidemic can be estimated.

Acknowledgments

Thanks to anonymous reviewers for providing comments and suggestions, which contributed to improving this paper.

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A The non-trivial equilibrium point

The second degree polynomial given by (11) has the coefficients given by combination of the parameters R_{ij} given by equation (4). By observing these parameters, it is obvious that $R_{11} < 1$, $R_{21} < 1$, and $R_{32} < 1$. The difference $(1 - R_{11})(1 - R_{21}) - R_{32}$ is written as

$$(1 - R_{11})(1 - R_{21}) - R_{32} = \frac{(\mu+\gamma)^2(\mu+\alpha)(\mu+\alpha+\eta k_1) + d_1 + d_2}{(\mu+\gamma)^2(\mu+\alpha+\xi)[\mu+\alpha+\eta(k_1+k_2)]} > 0,$$

where

$$\begin{cases} d_1 = \xi(\mu+\gamma)[\mu(\mu+\alpha+\eta k_1) + q\gamma(\mu+\alpha)] \\ d_2 = \eta k_2\{[(\mu+\gamma)(\mu+\alpha) + \mu\xi](\mu+p\gamma) + q(1-p)\mu\gamma\xi\}, \end{cases}$$

showing that $R_{32}/[(1 - R_{11})(1 - R_{21})] < 1$. Therefore, we have

$$\begin{cases} [R_{10}(1 - R_{21}) + R_{20}(1 - R_{11}) + R_{31}] > 0 \\ (1 - R_{11})(1 - R_{21})\left[1 - \frac{R_{32}}{(1-R_{11})(1-R_{21})}\right] > 0 \end{cases}$$

and $Pol(s)$ has 0 or 2 positive roots according to the Descartes' rule of signs.

However, the discriminant of the second-degree polynomial $Pol(s)$ is

$$\begin{aligned} \Delta &= [R_{10}(1 - R_{21}) + R_{20}(1 - R_{11}) + R_{31}]^2 - 4R_{10}R_{20}[(1 - R_{11})(1 - R_{21}) - R_{32}] \\ &= [R_{10}(1 - R_{11}) - R_{20}(1 - R_{21}) + R_{31}]^2 + 4R_{20}[R_{10}R_{32} + R_{31}(1 - R_{11})] > 0, \end{aligned}$$

hence, it has two positive solutions given by equations (5) and (6) in the main text. However, only the small solution s_s^* has biological meaning, and the big solution s_b^* does not have. This fact can be seen from equation (2), the coordinate of individuals with drug-sensitive tuberculosis i_1^* is always positive, but i_2^* is not. Rewriting the coordinate of individuals with drug-resistant tuberculosis i_2^* as

$$i_2^* = \frac{(\mu+\alpha+\xi)(\mu+\gamma)}{\gamma[\eta(k_1+pk_2) + p\beta_2 s^*]} R_{10}(s^m - s^*)\, i_1^*,$$

$i_2^* > 0$ if $s^m > s^*$, and $i_2^* < 0$ if $s^m < s^*$, where $s^m = (1 - R_{11})/R_{10}$. The second-degree polynomial $Pol(s)$ with upward concavity evaluated at this value is

$$Pol\left(s^m\right) = -\left[\frac{R_{31}}{R_{10}}\left(1 - R_{11}\right) + R_{32}\right] < 0,$$

which implies that s^m situates between small and big roots of $Pol(s)$, or, $s_s^* < s^m < s_b^*$. Therefore, $i_2^* > 0$ only for the small solution s_s^*, and all coordinates of P^* are positive, implying that there is a unique non-trivial equilibrium point. Summarizing, s_s^* has biological meaning $(i_2^*(s_s^*) > 0)$, but s_b^* does not have $(i_2^*(s_b^*) < 0)$.

Notice that R_{10} and R_{20} are the basic reproduction numbers of drug-sensitive and resistant strains of *M. tuberculosis*, and R_{11} and R_{21} are the additional reproduction numbers of drug-sensitive and resistant strains of *M. tuberculosis*. Finally, R_{31} and R_{32} are the additional reproduction numbers of a resistant strain of *M. tuberculosis* passing through a sensitive strain. (The interpretations of R_{ij} are given in Appendix B.)

Particular solutions of s_s^* given by equation (5) is obtained having didactical purpose. Let only drug-sensitive or resistant strain of *M. tuberculosis* transmission be considered in the solution of $Pol(s) = 0$.

Firstly, letting $\beta_2 = 0$ (hence $R_{20} = 0$ and $R_{31} = 0$), tuberculosis transmission among individuals is due only by those infected by drug-sensitive strain (i_1^*), due to the assumption that individuals infected by drug-resistant strain (i_2^*) originated from failure of drug administration are not transmitting. In this case, the fraction of susceptible individuals is

$$s_s^* = \frac{1 - R_{11}}{R_{10}}\left[1 - \frac{R_{32}}{\left(1 - R_{11}\right)\left(1 - R_{21}\right)}\right], \tag{A.1}$$

showing that the additional decrease in susceptibles, given by $R_{32}/\left[\left(1 - R_{11}\right)\left(1 - R_{21}\right)\right]$, is due to the failure of treatment, resulting in non-transmissible (by assumption) infected individuals with a drug-resistant strain. If a failure in the treatment does not occur, that is, $R_{32} = 0$, then the fraction of susceptibles become

$$s_s^* = \frac{1 - R_{11}}{R_{10}} = \frac{1}{R_{10}} - \frac{R_{11}}{R_{10}}, \tag{A.2}$$

and drug-resistant *M. tuberculosis* is not circulating.

Now, letting $\beta_1 = 0$ (hence $R_{10} = 0$), tuberculosis transmission among individuals is due only by those infected by drug-resistant strain (i_2^*), due to the assumption that individuals infected by drug-sensitive strain (i_1^*) are not transmitting. In this case, the fraction of susceptibles is

$$s_s^* = \frac{1 - R_{21}}{R_{20}}\left[1 - \frac{R_{32}}{\left(1 - R_{11}\right)\left(1 - R_{21}\right)}\right]\frac{1}{1 + \frac{R_{31}}{R_{20}\left(1 - R_{11}\right)}}, \tag{A.3}$$

it is showing again that the additional decrease in susceptibles, given by $R_{32}/\left[\left(1 - R_{11}\right)\left(1 - R_{21}\right)\right]$, is due to the failure of treatment, resulting in non-transmissible (by assumption) infected individuals with drug-sensitive strain. In this case, however, a second additional decrease in

susceptibles appears, given by $1/\{1+R_{31}/[R_{20}(1-R_{11})]\}$, due to the passage from i_1 to i_2. If a failure in treatment and the passage from i_1 to i_2 do not occur, that is $R_{32}=R_{31}=0$, the fraction of susceptibles becomes

$$s_s^* = \frac{1-R_{21}}{R_{20}} = \frac{1}{R_{20}} - \frac{R_{21}}{R_{20}}, \tag{A.4}$$

similar to equation (A.2), and drug-sensitive *M. tuberculosis* is not circulating.

Notice that when $R_{31}=R_{32}=0$, the dynamics of drug-sensitive and resistant strains of tuberculosis transmissions are decoupled, and each one can be dealt with separately.

B Interpretations of R_{ij}

In [5] neither the gross reproduction number nor the fraction of susceptible individuals were obtained. Hence, the interpretations of R_{ij} given by equation (4) are done.

A. Drug-sensitive tuberculosis transmission $R_1 = R_{10} + R_{11}$.

1. $R_{10} = \dfrac{\gamma}{\mu+\gamma} \times \dfrac{\beta_1}{\mu+\alpha+\xi}$. A primary drug-sensitive infectious individual survives the exposed class e_1 $(\gamma/(\mu+\gamma))$, and during the infectious period in i_1 generates drug-sensitive secondary cases $(\beta_1/(\mu+\alpha+\xi))$.

2. $R_{11} = \dfrac{\xi}{\mu+\alpha+\xi}(1-q)\dfrac{\gamma}{\mu+\gamma}$. A secondary drug-sensitive infectious individual survives the infectious class i_1 $(\xi/(\mu+\alpha+\xi))$, and a fraction $1-q$ goes back to exposed class e_1, surviving this class $(\gamma/(\mu+\gamma))$ returns to infectious class i_1 and generates new cases of sensitive tuberculosis.

B. Drug-resistant tuberculosis transmission $R_2 = R_{20} + R_{21}$.

1. $R_{20} = \dfrac{\gamma}{\mu+\gamma}(1-p)\dfrac{\beta_2}{\mu+\alpha+\eta(k_1+k_2)}$. A primary drug-resistant infectious individual survives the exposed class e_2 $(\gamma/(\mu+\gamma))$, and a proportion $1-p$ enters to i_2, and during the infectious period generates drug-resistant secondary cases $(\beta_2/[\mu+\alpha+\eta(k_1+k_2)])$.

2. $R_{21} = \dfrac{\eta k_2}{\mu+\alpha+\eta(k_1+k_2)}\dfrac{\gamma}{\mu+\gamma}(1-p)$. A secondary drug-resistant infectious individual survives the infectious class i_2 $(\eta k_2/[\mu+\alpha+\eta(k_1+k_2)])$, goes back to exposed class e_2 and survives this class $(\gamma/(\mu+\gamma))$, and a fraction $1-p$ returns to infectious class i_2 and generates new cases of resistant tuberculosis.

C. Drug-resistant tuberculosis transmission through drug-sensitive transmission $R_3 = R_{31} + R_{32}$.

1. $R_{31} = \dfrac{\gamma}{\mu+\gamma} p \dfrac{\xi}{\mu+\alpha+\xi} q \dfrac{\beta_2}{\mu+\alpha+\eta\left(k_1+k_2\right)}$. A primary drug-resistant infectious individual survives the exposed class e_2 $(\gamma/\left(\mu+\gamma\right))$, a proportion p enters to i_1, surviving this class $(\xi/\left(\mu+\alpha+\xi\right))$ a fraction q goes direct to infectious class i_2, and during the infectious period generates drug-resistant secondary cases $(\beta_2/\left[\mu+\alpha+\eta\left(k_1+k_2\right)\right])$.

2. $R_{32} = \dfrac{\eta\left(k_1+pk_2\right)k_2}{\mu+\alpha+\eta\left(k_1+k_2\right)} \dfrac{\gamma}{\mu+\gamma} \dfrac{\xi}{\mu+\alpha+\xi} q$. This is split in R_{321} and R_{322}.

2.1. $R_{321} = \dfrac{\eta k_1}{\mu+\alpha+\eta\left(k_1+k_2\right)} \dfrac{\gamma}{\mu+\gamma} \dfrac{\xi}{\mu+\alpha+\xi} q$. A secondary drug-resistant infectious individual survives the infectious class i_2 $(\eta k_1/\left[\mu+\alpha+\eta\left(k_1+k_2\right)\right])$, goes back to exposed class e_1 and survives this class $(\gamma/\left(\mu+\gamma\right))$, and enters to infectious class i_1 and surviving this class $(\xi/\left(\mu+\alpha+\xi\right))$ a fraction q returns to infectious class i_2 and generates resistant tuberculosis.

2.2. $R_{322} = \dfrac{\eta k_2}{\mu+\alpha+\eta\left(k_1+k_2\right)} \dfrac{\gamma}{\mu+\gamma} p \dfrac{\xi}{\mu+\alpha+\xi} q$. A secondary drug-resistant infectious individual survives the infectious class i_2 $(\eta k_2/\left[\mu+\alpha+\eta\left(k_1+k_2\right)\right])$, goes back to exposed class e_2 and survives this class $(\gamma/\left(\mu+\gamma\right))$, and a fraction p enters to infectious class i_1, surviving this class $(\xi/\left(\mu+\alpha+\xi\right))$ a fraction q returns to infectious class i_2 and generates resistant tuberculosis.