Are the beginning and ending phases of epidemics provided by next generation matrices? – Revisiting drug sensitive and resistant tuberculosis model

Hyun Mo Yang

UNICAMP – IMECC – DMA
Praça Sérgio Buarque de Holanda, 651
CEP: 13083-859, Campinas, SP, Brazil

Abstract

In epidemiological modelings, the spectral radius of the next generation matrix evaluated at the trivial equilibrium was considered as the basic reproduction number. Also, the global stability of the trivial equilibrium point was determined by the left eigenvector associated to that next generation matrix. More recently, the fraction of susceptible individuals was also obtained from the next generation matrix. By revisiting drug sensitive and resistant tuberculosis model, the gross reproduction number and the fraction of susceptible individuals are calculated. Hence, the next generation matrices shed light to the evolution of the dynamics: the beginning of the epidemics via the reproduction number and the approaching to the epidemics level via the asymptotic fraction of susceptible individuals.

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

1 Introduction

In epidemiological modelings, in general, there is a unique threshold, which is called the basic reproduction number (denoted by $R_0$). This number is taken as the intensity at which epidemics spread out when one case is introduced in a completely susceptible population. Additionally,
by evaluating the equilibrium value of the fraction of susceptible individuals (denoted by \( s^* \)),
this quantity could be expressed as \( s^* = 1/R_0 \). In another words, the inverse of the basic
reproduction number predicts the final size of an epidemics. Remembering that the basic
reproduction number is obtained from the stability analysis of the trivial equilibrium point
(denoted by \( P_0 \), which describes the absence of epidemics), it is expected that both initial \( (R_0) \)
and final \( (s^*) \) phases of epidemics can be obtained from this analysis, and, as a consequence, it
is not necessary the calculation of the fraction of susceptible individuals \( s^* \) in the steady state.

One of the approaches to determine the stability of the trivial equilibrium point is evaluating
the spectral radius of the corresponding next generation matrix, which is taken as the
basic reproduction number \([2]\). Instead of this spectral radius, the basic reproduction number
is assumed to be the sum of the coefficients of the characteristic equation corresponding to the
next generation matrix, which was proposed in \([9]\) and proved in \([10]\). In susceptible - exposed
- infectious - recovered (SEIR) model, there are two distinct characteristic equations correspond-
ing to two different next generation matrices, but the sum of the coefficients results in the same
threshold, which is linked to the basic reproduction number \( R_0 \) (hence, the second threshold \( s^* \)
appears implicitly, see Discussion). But in SIR model, there is only one characteristic equation
resulting in a unique threshold, and the relationship \( s^* = 1/R_0 \) comes out from the steady
state value of the fraction of the susceptible individuals. However, some models taking into
account an additional route of infection besides the infection of susceptible from an infectious
individual presents two different thresholds. In \([9]\) two procedures were presented aiming the
calculation of these two thresholds, which are the gross reproduction number (denoted by \( R_g \),
with \( R_g = R_0 + R_a \), where \( R_a \) is an additional reproduction number) and the fraction of the
susceptible individuals \( s^* \). Due to appearance of two different thresholds, there is not the in-
verse relationship between gross reproduction number and fraction of susceptible individuals,
that is, \( s^* \neq 1/R_g \).

Hence, the next generation matrix can in fact shed light into two properties of the dynam-
ics: the beginning of the epidemics via the reproduction number and the approaching to the
epidemics level via the asymptotic fraction of susceptible individuals. The goal of this paper
is the description of these two distinct phases of an epidemics, which is possible if next gen-
eration matrix could be constructed in different ways. In order to show that the beginning
(introduction of infection) and the asymptotic level (final size) of epidemics are provided by
different next generation matrices, drug sensitive and resistant tuberculosis transmission model
is revisited \([6]\). That model was analyzed numerically, which is the reason behind this revisiting
aiming the calculation of both thresholds, which involves a quite complex manner to evaluate
them.

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

The ineffective treatment of tuberculosis leads to emergence of multidrug resistant (MDR) *Mycobacterium tuberculosis* to the two most potent first-line medications (isoniazid and rifampin) [4]. Tuberculosis is responsible for the most deaths worldwide, and in 2017, MDR tuberculosis contributed to 14% of these deaths globally [5].

2.1 Revisiting drug sensitive and resistant tuberculosis model

In [6] a tuberculosis transmission model was proposed including drug treatment. They assumed that failure in treatment can arise drug resistant *M. tuberculosis*, resulting in model

\[
\begin{align*}
\frac{ds}{d\tau} &= \mu - \beta_1 i_1 s - \beta_2 i_2 s - \mu s \\
\frac{de_1}{d\tau} &= \beta_1 i_1 s + (1 - q) \xi i_1 + \eta k_1 i_2 - (\mu + \gamma) e_1 \\
\frac{di_1}{d\tau} &= \gamma e_1 + p \gamma e_2 - (\mu + \alpha + \xi) i_1 \\
\frac{de_2}{d\tau} &= \beta_2 i_2 s + \eta k_2 i_2 - (\mu + \gamma) e_2 \\
\frac{di_2}{d\tau} &= (1 - p) \gamma e_2 + q \xi i_1 - [\mu + \alpha + \eta (k_1 + k_2)] i_2,
\end{align*}
\]

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 [6]). The drug sensitive and drug resistant transmission rates are $\beta_1$ and $\beta_2$. Parameters $\mu$ and $\alpha$ are the natural and tuberculosis induced mortality rates; $\gamma$ is the endogenous reactivation rate; $\xi$ and $\eta$ 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 [6], the authors obtained a threshold applying M-matrix theory, however, neither gross reproduction number nor the fraction of susceptible individuals were obtained. Tuberculosis modeling considering drug sensitive and drug resistant strains presents a little bit complex calculation of both thresholds.

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

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

and the non-trivial equilibrium $P^*$, or endemic equilibrium, given by
\[ P^* = (s = s^*, \bar{e}_1 = e_1^*(s^*), \bar{i}_1 = i_1^*(s^*), \bar{e}_2 = e_2^*(s^*), \bar{i}_2 = i_2^*(s^*)) \]

with coordinates (they are written as a function of \( s^* \)) being given by

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

(2)

where the fraction of susceptible individuals \( s^* \) is positive solution of \( Pol(s) = 0 \), a second degree polynomial given by

\[
Pol(s) = R_{10} R_{20} s^2 - [R_{10} (1 - R_{21}) + R_{20} (1 - R_{11}) + R_{31}] s + (1 - R_{11}) (1 - R_{21}) \left[ 1 - \frac{R_{32}}{(1 - R_{11}) (1 - R_{21})} \right],
\]

(3)

with the parameters \( R_{ij} \) being given by

\[
\begin{align*}
    R_{10} & = \frac{\gamma}{\mu + \gamma} \frac{\beta_1}{\mu + \alpha + \xi} \quad \text{and} \quad R_{11} = \frac{\xi}{\mu + \gamma} \frac{(1-q) \gamma}{\mu + \gamma} \\
    R_{20} & = \frac{\gamma}{\mu + \gamma} (1-p) \frac{\beta_2}{\mu + \alpha + \eta (k_1 + k_2)} \quad \text{and} \quad R_{21} = \frac{\mu + \alpha + \eta (k_1 + k_2)}{\mu + \alpha + \eta (k_1 + k_2)} \frac{\gamma}{\mu + \gamma} (1-p) \\
    R_{31} & = \frac{\gamma}{\mu + \gamma} p \frac{\xi}{\mu + \alpha + \eta (k_1 + k_2)} \quad \text{and} \quad R_{32} = \frac{\gamma}{\mu + \gamma} p \frac{\xi}{\mu + \gamma} (1-p).\end{align*}
\]

(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

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

where

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

showing that \( R_{32} / [(1 - R_{11}) (1 - R_{21})] < 1 \). Notice that \( R_{10} \) and \( R_{20} \) are the basic reproduction numbers of drug sensitive and resistant strains of \( M. \text{tuberculosis} \), and \( R_{11} \) and \( R_{21} \) are the additional reproduction numbers of drug sensitive and resistant strains of \( M. \text{tuberculosis} \). Finally, \( R_{31} \) and \( R_{32} \) are the additional reproduction numbers of resistant strain of \( M. \text{tuberculosis} \) passing through sensitive strain. (See Appendix A for interpretation of \( R_{ij} \).)
In a transmission model of drug sensitive and resistant *M. tuberculosis*, $s^*$ is calculated from the equation $Pol(s) = 0$, with $Pol(s)$ being given by equation (3), whose discriminant is

$$
\Delta = \left[R_{10} (1 - R_{21}) + R_{20} (1 - R_{11}) + R_{31}\right]^2 - 4R_{10}R_{20} \left[(1 - R_{11}) (1 - R_{21}) - R_{32}\right]
\]
$$

$$
= \left[R_{10} (1 - R_{11}) - R_{20} (1 - R_{21}) + R_{31}\right]^2 + 4R_{20} \left[R_{10}R_{32} + R_{31} (1 - R_{11})\right] > 0.
$$

Hence, it has always two positive solutions, where the small one is given by

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

which is biologically feasible. The big solution $s^*_b$, given by

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

does not have biological meaning, which can be noticed from equation (2). The coordinate of individuals with drug sensitive tuberculosis $i_1^*$ is always positive, but, Rewriting the coordinate of individuals with drug resistant tuberculosis $i_2^*$ as

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

it is positive whenever $s^* < s^m$, where $s^m = (1 - R_{11}) / R_{10}$. However, evaluating $Pol(s)$ at this value, $Pol(s^m)$ is

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

which implies that $s^m$ situates between small and big solutions of $Pol(s) = 0$, or, $s^*_a < s^m < s^*_b$, resulting in $i_2^*(s^*_a) > 0$ and $i_2^*(s^*_b) < 0$. Hence, all coordinates of $P^*$ are positive only for small solution $s^*_a$, implying that there is a unique non-trivial equilibrium point.

Let only drug sensitive or resistant strain of *M. tuberculosis* transmission be considered. This has didactical purpose only (actually, it does not occur).

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

$$
s^* = \frac{1 - R_{11}}{R_{10}} \left[1 - \frac{R_{32}}{\left(1 - R_{11}\right) (1 - R_{21})}\right], \tag{7}
$$

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

$$
s^* = \frac{1 - R_{11}}{R_{10}} = \frac{1}{R_{10}} - \frac{R_{11}}{R_{10}}, \tag{8}
$$
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

$$s^* = \frac{1 - R_{21}}{R_{20}} \left[ 1 - \frac{R_{32}}{(1 - R_{11})(1 - R_{21})} \right] \frac{1}{1 + \frac{R_3}{R_{20}(1 - R_{11})}},$$

(9)

showing again that the additional decreasing in susceptibles, given by $R_{32}/[(1 - R_{11})(1 - R_{21})]$, 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 decreasing 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 failure in treatment and passage from $i_1$ to $i_2$ do not occur, that is $R_{31} = R_{32} = 0$, the fraction of susceptibles becomes

$$s^* = \frac{1 - R_{21}}{R_{20}} = \frac{1}{R_{20}} - \frac{R_{21}}{R_{20}},$$

(10)

similar to equation (8), 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.

### 2.2 Thresholds – $R_g$ and $s^*$

In preceding section, the fraction of susceptible individuals at endemic equilibrium $s^*$ 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, respectively, $F$ and $V$ evaluated at the trivial equilibrium are obtained, resulting in the next generation matrix $FV^{-1}$.

In drug sensitive and resistant tuberculosis transmissions model, there are several next generation matrices. Only two next generation matrices evaluated at the trivial equilibrium $P^0$ are considered, with the matrices being obtained from the vector of variables $x = (e_1, i_1, e_2, i_2)^T$, where superscript $T$ stands for the transposition of a matrix.

#### 2.2.1 The gross reproduction number $R_g$

In order to obtain the basic reproduction number, diagonal matrix $V$ is considered. Hence, the vectors $f$ and $v$ are

$$f = \begin{pmatrix} \beta_1 i_1 s + (1 - q) \xi i_1 + \eta k_1 i_2 \\ \gamma e_1 + p \gamma e_2 \\ \beta_2 i_2 s + \eta k_2 i_2 \\ (1 - p) \gamma e_2 + q \xi i_1 \end{pmatrix}$$

and

$$v = \begin{pmatrix} (\mu + \gamma) e_1 \\ (\mu + \alpha + \xi) i_1 \\ (\mu + \gamma) e_2 \\ [\mu + \alpha + \eta (k_1 + k_2)] i_2 \end{pmatrix}.$$
from which we obtain the matrices $F$ and $V$ given by

$$
F = \begin{bmatrix}
0 & \beta_1 + (1 - q) \xi & 0 & \eta k_1 \\
\gamma & 0 & p \gamma & 0 \\
0 & 0 & \beta_2 + \eta k_2 \\
0 & q \xi & (1 - p) \gamma & 0
\end{bmatrix}
$$

and

$$
V = \begin{bmatrix}
\mu + \gamma & 0 & 0 & 0 \\
0 & \mu + \alpha + \xi & 0 & 0 \\
0 & 0 & \mu + \gamma & 0 \\
0 & 0 & 0 & \varphi
\end{bmatrix},
$$

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

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

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

$$
(\lambda^2 - R_1) (\lambda^2 - R_2) - R_3 \lambda = 0,
$$

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

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

with $R_{ij}$ being given by equation (4). According to [9], the gross reproduction number $R_g$ is given by

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

where max stands for the maximum value among them. Notice that the spectral radius $\rho$ cannot be obtained analytically.

The condition to the trivial equilibrium point $P^0$ 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.

Let two cases be considered. Firstly, consider $R_{32} = 0$, that is, there is not failure in treatment, or $R_{31} = 0$, that is, there is not passage from $i_1$ to $i_2$. In this case, $R_g$ is

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

showing that drug sensitive and resistant strains of tuberculosis can reach endemic level even when $R_1 < 1$ and $R_2 < 1$, but $R_{31}/[(1 - R_1) (1 - R_2)] > 1$ or $R_{32}/[(1 - R_1) (1 - R_2)] > 1$. The joint propagation of drug sensitive and resistant strains facilitates the persistence of epidemics.
However, if $R_{32} = 0$ and $R_{31} = 0$, $R_g$ is

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

both strains propagate independently. Notice that if $R_1 > 1$ and $R_2 < 1$, drug sensitive tuberculosis is in endemic level, but drug resistant tuberculosis goes to extinction, and vice-versa if $R_1 < 1$ and $R_2 > 1$.

### 2.2.2 The fraction of susceptible individuals $s^*$

In order to obtain the fraction of susceptible individuals, infection matrix $M$ must be the simplest (matrix with least number of non-zeros). Hence, the vectors $f$ and $v$ are

$$f = \begin{pmatrix} \beta_1 i_1 s \\ \beta_2 i_2 s \\ 0 \end{pmatrix} \quad \text{and} \quad v = \begin{pmatrix} -(1-q)\xi_1 - \eta k_1 i_2 + (\mu + \gamma) e_1 \\ -\gamma e_1 - p \gamma e_2 + (\mu + \alpha + \xi) i_1 \\ -\eta k_2 i_2 + (\mu + \gamma) e_2 \\ -(1-p)\gamma e_2 - q \xi_1 + [\mu + \alpha + \eta (k_1 + k_2)] i_2 \end{pmatrix},$$

from which we obtain the matrices $F$ and $V$ given by

$$F = \begin{bmatrix} 0 & \beta_1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta_2 \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} -\eta k_1 \\ 0 \\ -\eta k_2 \\ -\xi \end{bmatrix}.$$

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 $\chi_4 = \beta_2 n_{31}$,

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

where $\chi_i$ are given by ($p \neq 0$)

$$\chi_1 = \frac{R_{10}}{1 - R_{11}} \left( 1 - \frac{R_{32}}{(1 - R_{11})(1 - R_{21})} \right)^{-1},$$

$$\chi_2 = \frac{R_{20} (1 - R_{11}) + R_{31}}{(1 - R_{11})(1 - R_{21})} \left( 1 - \frac{R_{32}}{(1 - R_{11})(1 - R_{21})} \right)^{-1},$$

$$\chi_3 = \frac{p}{1 - R_{11} \frac{1}{1+p} R_{33}} \left( 1 - \frac{R_{32}}{(1 - R_{11})(1 - R_{21})} \right)^{-1},$$

$$\chi_4 = \frac{1}{p} \frac{R_{20} (1 - R_{11}) + R_{31}}{(1 - R_{11})(1 - R_{21})} \left( 1 - \frac{R_{32}}{(1 - R_{11})(1 - R_{21})} \right)^{-1}.$$
with $R_{ij}$ being given by equation (4), and 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 $s^*$ nor in the gross reproduction number $R_g$.

The characteristic equation (14) has two equal eigenvalues $\lambda = 0$, and other two are given by solutions of

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

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 is the big solution, that is,

$$\rho = \frac{\chi_1 + \chi_2 + \sqrt{(\chi_1 + \chi_2)^2 - 4 (\chi_1 \chi_2 - \chi_3 \chi_4)}}{2}. \quad (16)$$

Hence, the trivial equilibrium point $P_0$ is LAS if $\rho < 1$, and $\rho$ is a threshold.

It is clear that this new threshold $\rho$, given by equation (16), can not be associated with the gross reproduction number $R_g$, given by equation (13). To clarify the appearance of a second threshold, let, as the previous section, two special cases be considered.

Firstly, when $\beta_2 = 0$ ($\chi_2 = \chi_4 = 0$), the spectral radius of equation (14) is $\rho_1$, and equation (16) becomes

$$\rho_1^{-1} = \frac{1 - R_{11}}{R_{10}} \left[ 1 - \frac{R_{32}}{(1 - R_{11})(1 - R_{21})} \right]. \quad (17)$$

Comparing $\rho_1$ with equation (7), it is clear that $\rho_1 = 1/s^*$. When $\beta_1 = 0$ ($\chi_1 = \chi_3 = 0$), the spectral radius of equation (14) is $\rho_2$, and equation (16) becomes

$$\rho_2^{-1} = \frac{(1 - R_{11})(1 - R_{21})}{R_{20} (1 - R_{11}) + R_{31}} \left[ 1 - \frac{R_{32}}{(1 - R_{11})(1 - R_{21})} \right]. \quad (18)$$

Comparing $\rho_2$ with equation (9), it is clear that $\rho_2 = 1/s^*$.

It is not an easy task to prove that $\rho = 1/s^*$, when $\beta_1 > 0$ and $\beta_2 > 0$, with $\rho$ and $s^*$ being given by equations, respectively, (16) and (3). The main reason is the parameter $R_{33}$ appearing in $\rho$ but not in $s^*$, but numerically $\rho = 1/s^*$ can be verified. Hence, the spectral radius is exactly the inverse of the fraction of susceptible individuals.

The condition to the trivial equilibrium point $P_0$ be LAS is $\rho < 1$. If $\rho > 1$, $P_0$ is unstable, and the unique non-trivial equilibrium point $P^*$ appears. Hence, $P^*$ is biologically feasible if $\rho > 1$, that is, $s^* < 1$, and $1/s^*$ is another threshold.

Finally, letting $R_{32} = 0$ besides $\beta_2 = 0$, the spectral radius (17) becomes

$$\rho_1^{-1} = \frac{1 - R_{11}}{R_{10}}, \quad (19)$$
which is equal to the fraction of susceptibles given by equation (8). 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 (18) becomes

$$\rho_{2}^{-1} = \frac{1 - R_{21}}{R_{20}},$$

which is equal to the fraction of susceptibles given by equation (11), and $R_{20}$ is the basic reproduction number of drug resistant strain, and $R_{21}$ is the additional reproduction number.

3 Discussion

Tuberculosis modeling considering sensitive and drug resistant M. tuberculosis transmissions was taken as an example of application of the next generation matrix to describe both the beginning and ending phases of epidemics.

Depending on the construction of vectors $f$ and $v$, consequently matrices $M$ and $V$, two thresholds are obtained from the characteristic equations corresponding to the next generation matrix $FV^{-1}$. Traditionally, the spectral radius was taken as the basic (gross) reproduction number [3] [8], but different approach was proposed in [9], which consists in summing the coefficients of the characteristic equation rather than evaluating the spectral radius. This approach has a substantial advantage: there is not necessity of a recipe to construct vectors $f$ and $v$ [7].

However, depending on the complexity of the model, the sum of the coefficients is not sufficient to determine the gross reproduction number. The model of tuberculosis revisited here is an example. The method used to obtain two thresholds $R_g$ and $1/s^*$ is summarized: Let the characteristic equation corresponding to next generation matrix $FV^{-1}$ be written as

$$\Lambda(\lambda) = \Lambda_n(\lambda)\Lambda_m(\lambda) - \Lambda_p(\lambda),$$

(20)

where $\Lambda_n(\lambda) = \lambda^n - a_{n-1}\lambda^{n-1} - \cdots - a_1\lambda - a_0$, $\Lambda_m(\lambda) = \lambda^m - b_{m-1}\lambda^{m-1} - \cdots - b_1\lambda - b_0$, 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 $v$ (matrix $F$ has the least number of non-zeros, while matrix $V$ has the most number of non-zeros), then the spectral radius $\rho = \rho(FV^{-1})$ of the characteristic equation $\Lambda(\lambda) = 0$ is the inverse of the fraction of susceptible individuals $s^*$, that is, $s^* = 1/\rho$.

(B) In all other constructions of vectors $f$ and $v$, the sum of the coefficients of the characteristic equation corresponding to the next generation matrix $FV^{-1}$ is the gross reproduction number $R_g$, that is,

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

(21)
where max stands for the maximum value among $\Omega_n$, $\Omega_m$ and $\Omega_p/\left[ (1 - \Omega_n)(1 - \Omega_m) \right]$. Hence, the best choice of construction of vectors $f$ and $v$ is such that the matrix $V$ must be diagonal.

Observe that equation (20) has at least two positive solutions (excluding the possibility of absence of positive solution). For this reason, the threshold in item (A) must be the spectral radius. However, if there are not interactions between pathogens or strains, that is, $\Lambda_p(\lambda) = 0$, then there is a unique positive solution for each equation $\Lambda_n(\lambda) = 0$ or $\Lambda_m(\lambda) = 0$, and $s^* = 1/\Omega_n$ or $s^* = 1/\Omega_m$, instead of spectral radius. This is called simplified item (A).

Notice that items (A) and (B) were cited in [9] but only item (B) was briefly exemplified (section 2.2.1 is direct application of this item). Here, more details regarding the application of item (B) in tuberculosis modeling encompassing drug sensitive and resistant strains were presented, and item (A) is a novel application.

Item (A) dealing with the fraction of susceptible individuals deserves some comments. The steady state fraction of susceptible individuals is obtained as the roots of the second degree polynomial (4), which has two positive solutions. It was shown that only the small one was chosen due to biological meaning (the big solution generates negative coordinates for the non-trivial equilibrium). The stability of the trivial equilibrium point is assessed also by roots of a second degree polynomial, given by the characteristic equation (15) 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 $\rho$ must be chosen as the threshold.
2. The trivial equilibrium is locally asymptotically stable if the spectral radius is lower than one ($\rho < 1$), and unstable otherwise. Hence, epidemics is settle at the community if $\rho > 1$, that is, $s^* < 1$.

Hence, in epidemics situation, the spectral radius guarantees value higher than one, and, consequently, the inverse is lower than one. It is not an easy task to demonstrating analytically that the small solution of equation (15) is equal to the inverse of the spectral radius of characteristic equation (15), $s^*_s = 1/\rho$, but it can be verified numerically. However, in special cases, this relationship was demonstrated analytically.

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 (12), $R_1 = 6.4$, $R_2 = 3.7$ and $R_3 = 0.04$, and $R_{in} = 0.003$, where $R_{in} = R_{32}/\left[ (1 - R_1)(1 - R_2) \right]$. The small and big fraction of susceptible individuals are, from (5) and (6), $s^*_s = 0.1341$ and $s^*_b = 0.2537$. From equation (16), the inverse of spectral radius is $1/\rho = 0.1314$, while the inverse of small eigenvalue of equation (15) is 0.2537. Hence, the inverse of the spectral radius is equal to the small fraction of susceptible individuals, which value is in accordance with asymptotic value obtained by Runge-Kutta method.
It is worth stressing the fact that characteristic equations (11) and (14) have similar structure. However, the gross reproduction number is given by the sum of the coefficients of equation (13), while the inverse of the fraction of susceptible individuals is given by the spectral radius of equation (15).

The special case letting $\beta_2 = 0$ and $R_{32} = 0$ dealt with in preceding section is quite similar to that model considered by Driessche and Watmough [3]. In their analysis they did not realize the existence of two thresholds, for this reason they considered that the basic reproduction number is given by equation (19), not equation (12).

Is the spectral radius indeed the inverse of the fraction of susceptible individuals? Let two examples be considered, SEIR and dengue with transovarial transmission. In both examples, there is only one pathogen, hence $\Lambda_p(\lambda) = 0$ in equation (20), resulting in $\Lambda(\lambda) = \Lambda_n(\lambda)$, with $\Omega_n = \sum_{i=0}^{n-1} a_i$ and $\Lambda_n(\lambda) = 0$ has only one positive solution. For this reason, first threshold is $R_g = \Omega_n$, from equation (21), and second threshold is $s^* = 1/\Omega_n$, not the spectral radius. Hence, simplified item (A) must be applied.

Firstly, 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

$$\begin{align*}
\frac{d}{dt}s &= \mu - \beta si - \mu s \\
\frac{d}{dt}e &= \beta si - (\mu + \gamma) e \\
\frac{d}{dt}i &= \gamma e - (\mu + \sigma) i \\
\frac{d}{dt}r &= \sigma i - \mu r,
\end{align*}$$

(22)

where $s$, $e$, $i$ and $r$ are the fractions of, respectively, susceptible, exposed, infectious and recovered individuals. The model parameters are the mortality rate $\mu$, the contact rate $\beta$, the infectious ($\gamma$) and recovery ($\sigma$) rates.

The system of equations (22) has two equilibrium points: the trivial $P^0 = (1, 0, 0, 0)$ and the non-trivial $P^* = (s^*, e^*, i^*, r^*)$, where $s^* = 1/R_0$, with the basic reproduction number $R_0$ being given by

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

(23)

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

The basic reproduction number is obtained according to item (B), that is, the sum of the coefficients of the characteristic equation. The characteristic equation corresponding to the next generation matrix obtained from diagonal matrix $V$ is

$$\lambda^2 - R_0 = 0,$$

(24)

12
where the basic reproduction number $R_0$ is given by equation (23).

Let procedure stated in simplified item (A) be applied. The characteristic equation corresponding to the next generation matrix obtained from non-diagonal matrix $V$ is

$$\lambda (\lambda - R_0) = 0,$$

where $R_0$ is given by equation (23). According to simplified item (A), this full matrix $V$ must originate the second threshold $1/s^*$ as the sum of coefficients. Hence, the inverse of $R_0$ is the fraction of susceptible individuals, that is, $s^* = 1/R_0$ which appears implicitly. Notice in SEIR model the spectral radius is also $R_0$, that is, $\rho = R_0$.

Notice that in SEIR model, the spectral radius $\rho$ of equation (24) is $\rho = \sqrt{R_0}$, while the spectral radius of equation (25) is $\rho = R_0$. Notice that $\rho = R_0$ is the reason why some authors claim that the construction of vectors $f$ and $v$ according to simplified item (A) is correct [3].

But, the sum of coefficients of both equations is the same, that is, $\Omega_2 = R_0$. In SIR model, however, 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. Hence, the fraction of susceptible individuals being the inverse of the basic reproduction number appears only from the equilibrium value of $s^*$.

A second model is dengue encompassing transovarial transmission model [11], which is also revisited to illustrate the existence of two thresholds describing two extremes: beginning and ending of epidemics. In SEIR model, there is one pathogen, one population and one route of transmission, while in dengue with transovarial transmission model, there are two populations, one common pathogen, but two routes of transmission.

The model presented in [11] considered dengue virus being transmitted by both horizontal and transovarial transmission routes. That model was described by the system of differential equations

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

(26)

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 $l = l_1 + l_2$.

With respect to the model parameters, $\alpha$ is the proportion of transovarial transmission, $\mu_h$ is the birth and mortality rates of humans, and $\sigma_h$ is recovery rate. The per-capita oviposition
rate is \( \phi \), \( q \) and \( f \) are the fractions of eggs that are hatching to larva and that will originate female mosquitoes, respectively, \( C \) is the carrying capacity of the breeding sites, \( \sigma_a \) is rate at which larva become adults, and \( \mu_a \) and \( \mu_f \) are the mortality rates of, respectively, immatures and adults. Finally, \( \beta_h \) is the transmission coefficient from mosquito to human, and \( \beta_m \) is the transmission coefficient from human to mosquito.

The system of equations (26) has two equilibrium points, assuming that \( Q_0 > 1 \), where

\[
Q_0 = \frac{\sigma_a q f \phi}{[\sigma_a + \mu_a] \mu_f} \text{ is the basic offspring number.}
\]

The trivial equilibrium \( P_0 \), or disease free equilibrium, is given by

\[
P_0 = \left( \bar{l}_1 = l^* = C \left( 1 - \frac{1}{Q_0} \right), \bar{l}_2 = 0, \bar{m}_1 = m^* = \frac{\sigma_a}{\mu_f} C \left( 1 - \frac{1}{Q_0} \right), \bar{m}_2 = 0, \bar{s} = 1, \bar{i} = 0 \right),
\]

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

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

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

\[
s^* \times \frac{m_1^*}{m^*} = \frac{1 - R_v}{R_0} = \frac{1}{R_0} - \frac{\alpha}{R_0}.
\]

(see [11] for detailed calculations.) The gross reproduction number \( R_g \) is defined as

\[
R_g = R_0 + R_v,
\]

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

Only two next generation matrices evaluated at the trivial equilibrium \( P_0 \) are considered, 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.

In order to obtain the gross reproduction number, diagonal matrix \( V \) is considered, according to item (B). The next generation matrix \( F_1 V^{-1} \) is

\[
F V^{-1} = \begin{bmatrix}
0 & \frac{\sigma_a}{\mu_a + \mu_a} \frac{N R_0^m}{R_0} \\
\frac{1}{N} R_0^h & 0 \\
\alpha \frac{\sigma_a}{\mu_a + \mu_a} & 0 & 0
\end{bmatrix},
\]

and the corresponding characteristic equation is

\[
\lambda \left( \lambda^2 - R_g \right) = 0,
\]

with \( R_g \) being given by equation (29), which is the gross reproduction number (the sum of the coefficients of the characteristic equation). In transovarial dengue transmission model, there are other next generation matrices resulting in the same gross reproduction number (see [11]).
In order to obtain the fraction of susceptible individuals, infection matrix $M$ must be the simplest (matrix with least number of non-zeros), thus matrix $V$ is the most full with non-zero elements. In this case, the next generation matrix $FV^{-1}$ is

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

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

$$\lambda \left( \lambda^2 - \frac{R_0}{1-R_v} \right) = 0. \tag{31}$$

According to simplified item (A), the sum of the coefficients is a threshold, that is, $1/\Omega_3 = (1-R_v)/R_0$. Comparing, however, with equation (28), the product of the fractions of susceptible humans and mosquitoes is indeed the threshold, that is, $s^* \times m^*_1/m^* = (1-R_v)/R_0$. This threshold must be the product of susceptible populations, due to the fact that two populations are involved in the transmission.

Comparing equations (25) and (25) in SEIR model, the relationship $s^* = 1/R_0$ is obeyed, while, from equations (30) and (31), the product $s^* \times m^*_1/m^*$ is not inverse of $R_g$. Hence, two routes of transmission result 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 epidemics. Nevertheless, if the next generation matrix provides the initial strength of an epidemics, it is expected that it may also predict the final size of an epidemics, which is indeed measured by the remaining fraction of susceptible individuals – this fraction portrays the ending phase of an epidemics, that is, those individuals who have not been infected at 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 another words, how intense is an epidemics (higher $R_0$) more individuals are infected and low number of individuals are left uninfected, hence the fraction of susceptible individuals is low ($1/R_0$).

The procedures presented in [9] can be easily applied when the characteristic equation corresponding to the next generation matrix is given by equation (20), with $\Lambda_p(\lambda) = 0$. In this case, the sum of the coefficients of this equation is the basic (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 (20), then the gross reproduction number is given by equation (21), and the spectral radius is the inverse of the fraction of susceptible individuals. This case was shown revisiting drug sensitive and resistant tuberculosis transmission model.

It is worth stressing the fact that the sum of the coefficients of the characteristic equation of the next generation matrix provides only one threshold, by the fact that this equation has a unique positive eigenvalue. When there is not a unique positive eigenvalue, it is natural choosing the spectral radius for two reasons: (1) it is the greatest value assuming value higher than one to maintain epidemics, and, consequently, (2) the inverse of this number is the lowest, which is lower than one. In the case of the fraction of susceptible individuals, this number must be lower than one.

It is well accepted the fact that the basic (gross) reproduction number obtained from the next generation matrix is linked to the initial phase of an epidemics. Also, the global stability of the trivial equilibrium point could be determined by the left eigenvector associated to this next generation matrix [8]. Besides these two important results, the next generation matrix can predict the final size of an epidemics by allowing the calculation of the steady state fraction of susceptible individuals. Therefore, depending on how the next generation matrix is constructed, both initial and final phases of an epidemics can be estimated.

References

[1] R.M. Anderson, R.M. May, Infectious Diseases of Human. Dynamics and Control, Oxford University Press, Oxford, New York, Tokyo (1991).

[2] O. Diekmann, J.A.P. Heesterbeek, M.G. Roberts, The construction of next-generation matrices for compartmental epidemic models, J. R. Soc. Interface 7 (2010) 873-885.

[3] P. van den Driessche, J. Watmough, Reproduction number and sub-threshold endemic equilibria for compartmental models of disease transmission, Math. Biosc. 180(1-2) (2002) 29-48.

[4] T.R. Frieden, P.I. Fujiwara, R.M. Washko, M.A. Hamburg, Tuberculosis in New York City – turning the tide, N. Engl. J. Med. 333 (1995) 229-233.

[5] G.M. Knight, C.F. McQuaid, P.J. Dodd, R.M.G.J. Houben, Global burden of latent multirug-resistant tuberculosis: trends and estimates based on mathematical modelling, Lancet Infect. Dis. 19 (2019) 903-912.

[6] S.M. Raimundo, H.M. Yang, E. Venturino, Theoretical assessment of the relative incidence of sensitive and resistant tuberculosis epidemic in presence of drug treatment, Math. Biosc. Eng. 11(4) (2014) 971-993.

[7] M.G. Roberts, J.P.A. Heesterbeek, A new method to estimate the effort required to control an infectious disease. Proc. Royal Soc. London Series B 270 (2003) 1359-1364.
A Interpreting $R_{ij}$

In [6] 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. $R_{10} = \frac{\gamma}{\mu + \gamma} \times \frac{\beta_1}{\mu + \alpha + \xi}$. 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. $R_{11} = \frac{\xi}{\mu + \alpha + \xi} (1 - q) \frac{\gamma}{\mu + \gamma}$. 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. $R_{20} = \frac{\gamma}{\mu + \gamma} (1 - p) \frac{\beta_2}{\mu + \alpha + \eta (k_1 + k_2)}$. 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. $R_{21} = \frac{\eta k_2}{\mu + \alpha + \eta (k_1 + k_2)} \frac{\gamma}{\mu + \gamma} (1 - p)$. 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. \( R_{31} = \frac{\gamma p \xi q}{\mu + \gamma p \mu + \alpha + \xi} \cdot \frac{\beta_2}{\mu + \alpha + \eta (k_1 + k_2)}. \) A primary drug resistant infectious individual survives the exposed class \( e_2 (\gamma / (\mu + \gamma)) \), a proportion \( p \) enters to \( i_1 \), surviving this class \( (\xi / (\mu + \alpha + \xi)) \) a fraction \( q \) goes direct to infectious class \( i_2 \), and during the infectious period generates drug resistant secondary cases \( (\beta_2 / [\mu + \alpha + \eta (k_1 + k_2)]) \).

2. \( R_{32} = \frac{\eta (k_1 + p k_2) k_2}{\mu + \alpha + \eta (k_1 + k_2)} \cdot \frac{\gamma}{\mu + \gamma p \mu + \alpha + \xi} \cdot \frac{\xi q}{q}. \) This is split in \( R_{321} \) and \( R_{322} \).

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

2.2. \( R_{322} = \frac{\eta k_2}{\mu + \alpha + \eta (k_1 + k_2)} \cdot \frac{\gamma p \xi q}{q}. \) 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 \( p \) enters to infectious class \( i_1 \), surviving this class \( (\xi / (\mu + \alpha + \xi)) \) a fraction \( q \) returns to infectious class \( i_2 \) and generates resistant tuberculosis.