Number of infections suffered by a focal individual in a two-strain SIS-model with partial cross-immunity

E. Almaraz[a], A. Gómez-Corral[b,*]

[a] *Department of Statistics and Operations Research, School of Mathematical Sciences, Complutense University of Madrid, 28040-Madrid, Spain*
[b] *Instituto de Ciencias Matemáticas CSIC-UAM-UC3M-UCM, Calle Nicolás Cabrera 13-15, 28049-Madrid, Spain*

Abstract

We study a stochastic model for the spread of two pathogen strains –termed *type-1* and *type-2*– amongst a homogeneously mixing community consisting of a finite number of individuals. In the model we assume partial cross-immunity, exogenous streams of infection, and that the degree of severity of a newly infective individual depends on who this infective individual was infected by. The aim is to characterize the joint probability distribution of the numbers M_1 and M_2 of type-1 and type-2 infections suffered by a focal individual during an outbreak of the disease. We present iterative procedures for computing the probability mass function of (M_1, M_2) under the assumption that the initial state of the focal individual is known, and a numerical study of the model is performed to investigate the influence of certain key parameters on the spread of resistant bacteria in hospitals.

Keywords: Computational methods in Markov chains; Continuous-time Markov chains on discrete state spaces; Epidemiology

2000 MSC: Primary 60J28; Secondary 92D30

*Corresponding author

Email addresses: ealmarazluengo@mat.ucm.es (E. Almaraz), agcorral@ucm.es (A. Gómez-Corral)

URL: http://blogs.mat.ucm.es/agomez-corral (A. Gómez-Corral)

1. Introduction

Over the last decades, there have been numerous theoretical studies on the persistence and extinction of multiple pathogen strains in deterministic (see e.g. [1, 2], [3, Section 2.1], [19, Section 3], [25, 26], [27, Section 2]) and stochastic models (see e.g. [3, Section 2.2], [4, 6, 7, 8, 17], [19, Section 4], [27, Section 3]). These models involving several different strains of a pathogen have been applied to the study of the bacterial resistance to antibiotics [10, 12, 21], and diseases such as arenavirus and hantavirus [2], HIV/AIDS [9], HIV/TB [24], influenza [25], myxomatosis in rabbit populations [27], tuberculosis [11], and viral respiratory tract diseases [8], to name a few.

In the present paper the interest is in a stochastic SIS (*susceptible* $\rightarrow$ *infective* $\rightarrow$ *susceptible*) model with two strains –termed *type-1* and *type-2 strains*– and partial cross-immunity, which describes the spread of two competing pathogen strains amongst a homogeneously mixing community where co-infection is not permitted. Infective individuals are assumed to have different severities of disease (resulting in type-1 and type-2 infective individuals), and the severity of a newly infective individual depends on the severity of the infective individual it was infected by; then, the newly infective individual is immune to infection by the other strain during its infectious period, but it can be infected by any of the strains after becoming susceptible. Thus, we consider a two-strain SIS-model without co-infection, where the cross immunity is partial and, specifically, the protection of a type-k infective individual against infection by the strain of type k', with $k' \neq k$, is linked to its infectious period in such a way that there is no residual immunity after this infectious period ends.

The model is closely related to the IDS (*infector-dependent severity*) assumptions [7] allowing for two different severities, *mild* and *severe*, within the class of SIR (*susceptible* $\rightarrow$ *infective* $\rightarrow$ *removed*) epidemic models. The IDS-model is defined by Ball and Britton [7] by assuming that any susceptible contacted by a mildly (respectively, severely) infected individual becomes a mild case with probability $p_M^{(M)}$ (respectively, $p_M^{(S)}$), and a severe case with the remaining prob-

ability $p_S^{(M)} = 1 - p_M^{(M)}$ (respectively, $p_S^{(S)} = 1 - p_M^{(S)}$). Ball and Britton [7] use branching process and density-dependent population approximations to derive large-population properties of IDS-models with $p_M^{(M)} < 1$ and $p_S^{(S)} < 1$ and related vaccine-response models, and they point out that epidemics with either $p_M^{(M)} = 1$ or $p_S^{(S)} = 1$, such as the two-strain SIR-model investigated by Kendall and Saunders [19] under exponential distributional assumptions, have a more complex asymptotic behavior. For a related work, we refer the reader to the paper by Ball and Britton [5], who deal with a different epidemic model for varying severity by assuming that the degree of severity of an infective individual depends on the amount of infection force it has been exposed to. An interesting reference on two competing SIS epidemics is the work by Lopes and Luczak [23], where the spread of each strain in the absence of the other one is described by the stochastic logistic SIS epidemic model, and asymptotic results for the extinction time of the weaker strain are derived when one strain has a strictly larger basic reproductive ratio than the other, and the stronger strain on its own is supercritical.

The aim of this paper is to complement the treatment of the two-strain SIS-model with partial cross-immunity we started in [17, Section 3.2] –which can be seen as an IDS-model with $p_M^{(M)} = p_S^{(S)} = 1$– by focusing here on the numbers M_1 and M_2 of type-1 and type-2 infections suffered by a focal individual during an outbreak of the disease. To begin with, we define in Section 2 the underlying Markov chain model. In Section 3, we derive algorithmic solutions for the probability mass function of (M_1, M_2) when the initial state of the focal individual is known. Our analytical results are illustrated in Section 4 with reference to realistic data of Lipsitch et al. [21], and numerical examples are performed to investigate the effect of certain key parameters on the spread of antibiotic-sensitive and antibiotic-resistant bacterial strains in a hospital ward. Finally, some conclusions are given in Section 5.

2. The SIS-model with two strains and partial cross-immunity

We consider a homogeneously mixing population of N individuals divided into susceptible individuals and infective individuals; see Figure 1. The infective individuals are further subdivided into two types, termed type-1 and type-2 infective individuals, as a consequence of the spread of two strains that differ in their infectivities. It is assumed that the strains are perfectly distinguishable, and instantly diagnosed, and neither coinfection nor superinfection is possible. Each type-k infective individual, for $k \in \{1, 2\}$, remains infectious for an exponentially distributed random time with mean $\gamma_k^{-1} < \infty$, and then becomes again susceptible to either infection strain. When infected, each type-k infective individual transmits the strain that it itself is infected with by making contacts at the points of a homogeneous Poisson process of rate $\beta_k > 0$, in such a way that each contact is with an individual chosen uniformly at random from the subpopulation of susceptible individuals at the contact time, independently of other events. There is a possibility of exogenous infections and, irrespectively of other events, each susceptible individual may become infective of type k at the points of a homogeneous Poisson process of rate $\lambda_k \geq 0$, for $k \in \{1, 2\}$. The infectious period and contact process of each infective individual are independent of one another, regardless of its infectivity; and the infectious periods and contact processes of distinct infective individuals, and the exogenous processes of distinct susceptible individuals are all assumed to be mutually independent.

At time t, the population consists of $S(t)$ susceptible individuals, and $I_k(t)$ type-k infective individuals, for $k \in \{1, 2\}$, which results in $S(t) = N - I_1(t) - I_2(t)$ due to the assumption that there are no births, deaths or migrations. This means that the state of the population can be described by the vector $(I_1(t) + I_2(t), I_2(t))$, which takes values in the state space $\mathcal{S} = \cup_{i=0}^{N} l(i)$ with $l(i) = \{(i, j) : j \in \{0, ..., i\}\}$, for $i \in \{0, ..., N\}$; i.e., states in $l(i)$ are related to a population consisting of $I_1(t)+I_2(t) = i$ infective individuals and, consequently, $S(t) = N-i$ susceptible individuals. Specifically, the dynamics of the population

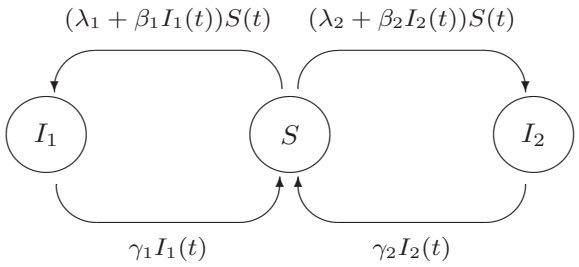

Figure 1: Compartmental diagram of the SIS-model with two strains and partial cross-immunity. A susceptible individual becomes infective of type k with rate $(\lambda_k + \beta_k I_k(t))S(t)$ and $S(t) = N - I_1(t) - I_2(t)$, and a type-$k$ infective individual becomes susceptible with rate $\gamma_k I_k(t)$, for $k \in \{1, 2\}$.

are driven by the non-null infinitesimal rates

$$q_{(i,j),(i',j')} = \begin{cases} (N-i)(\lambda_1 + (i-j)\beta_1), & \text{if } i' = i+1,\ j' = j, \\ (N-i)(\lambda_2 + j\beta_2), & \text{if } i' = i+1,\ j' = j+1, \\ (i-j)\gamma_1, & \text{if } i' = i-1,\ j' = j, \\ j\gamma_2, & \text{if } i' = i-1,\ j' = j-1, \end{cases} \tag{1}$$

and $q_{(i,j),(i,j)} = -q_{(i,j)}$ with

$$q_{(i,j)} = (N-i)(\lambda_1 + \lambda_2 + (i-j)\beta_1 + j\beta_2) + (i-j)\gamma_1 + j\gamma_2,$$

for $(i, j) \in \mathcal{S}$. By conveniently labeling states, (1) results in distinct level-dependent quasi-birth-death (LD-QBD) processes, which are used by Gómez-Corral and López-García [17, Section 3.2] to provide the sensitivities and elasticities of first-passage times and hitting probabilities, extreme values and stationary measures of either an outbreak of the disease or the outbreak of the type-k strain, for $k \in \{1, 2\}$.

3. Number of infections suffered by a focal individual

Assume that an outbreak starts at time $t = 0$ with $I_1(0)+I_2(0) \in \{1, 2, ..., N-1\}$ infective individuals and mark one of the $N-I_1(0)-I_2(0)$ susceptible individuals in the population. The statistics in which we are interested are the numbers

M_1 and M_2 of type-1 and type-2 infections suffered by the focal individual during the interval $(0, T_{i,j}]$, where $T_{i,j}$ denotes the random length of the residual outbreak when $(I_1(0) + I_2(0), I_2(0)) = (i, j)$, for initial states $(i, j) \in \cup_{i'=1}^{N-1} l(i')$; i.e., $T_{i,j} = \inf\{t > 0 : I_1(t) + I_2(t) = 0\}$ and it is thus related to the ultimate extinction of both strains. In the case of initial states $(i, j) \in l(i')$ with $i' = 0$, it is assumed that $(M_1, M_2) = (0, 0)$ almost surely.

Remark 1. It is important to remark that, starting with $i - j$ type-1 infective individuals and j type-2 infective individuals, the length $T_{i,j}$ of the residual outbreak amounts to a phase-type random variable of order $L = 2^{-1}N(N + 3)$ and representation $(\alpha_{i,j}, \mathbf{T})$, where $\mathbf{T}$ is a square matrix of order L consisting of infinitesimal rates linked to transitions between states of the class $\cup_{i'=1}^{N} l(i')$ of transient states; see e.g. Latouche and Ramaswami [20, Chapter 2]. By assuming a lexicographical ordering of states, the initial probability vector $\alpha_{i,j}$ of the LD-QBD process $\{(I_1(t)+I_2(t), I_2(t)) : t \geq 0\}$ is given by $\alpha_{i,j} = \mathbf{e}_L(2^{-1}i(i+1)+ j)$ and the nth moment of $T_{i,j}$ is readily derived as $E[T_{i,j}^n] = n!\alpha_{i,j}(-\mathbf{T}^{-1})^n\mathbf{1}_L$, where $\mathbf{e}_a(b)$ is a row vector of order a such that all entries are equal to 0, except for the bth entry which is equal to 1, and $\mathbf{1}_a$ is the unit vector of order a.

In analyzing the joint distribution of (M_1, M_2), we proceed to evaluate in a more general setting the conditional probabilities $P_{i,j,k}(m_1, m_2)$ that, starting at any arbitrary time t with $(I_1(t), I_2(t)) = (i - j, j)$ infective individuals and the focal individual at state k (with $k = 0$ if it is susceptible, and 1 and 2 if it is infective of type 1 and 2, respectively), the numbers M_1 and M_2 of type-1 and type-2 infections suffered by the focal individual during $(t, t + T'_{i,j,k}]$ are equal to m_1 and m_2, respectively, where $T'_{i,j,k}$ denotes the random length of the residual outbreak when the state of the focal individual at time t is given by k and $(I_1(t) + I_2(t), I_2(t)) = (i, j)$, for integers $k \in \{0, 1, 2\}$ and states $(i, j) \in \cup_{i'=1}^{N-1} l(i')$. It is clear that $T'_{i,j,k}$ is identically distributed to $T_{i,j}$, regardless of the integer $k \in \{0, 1, 2\}$, and the joint distribution of (M_1, M_2) depends on the *current* state of $\mathcal{X}$ and the state of the focal individual at time t only in terms of

(i,j,k), since $\mathcal{X}$ is time-homogeneous. By observing that the focal individual is chosen uniformly at random from the subpopulation of susceptible individuals at time $t=0$, the joint distribution of (M_1,M_2) can be then characterized from the conditional probabilities $\{P_{i,j,0}(m_1,m_2):(m_1,m_2)\in\mathbb{N}_0\times\mathbb{N}_0\}$, provided that $(I_1(0)+I_2(0),I_2(0))=(i,j)$ with $(i,j)\in\cup_{i'=1}^{N-1}l(i')$. For later use, we let $\mathcal{P}(m_1,m_2)$ be the family of conditional probabilities

$$\bigcup_{k=0}^{2}\{P_{i,j,k}(m_1,m_2):i\in\{1,...,N-\delta_{0,k}\},j\in\{\delta_{2,k},...,i-\delta_{1,k}\}\},$$

for each fixed pair $(m_1,m_2)\in\mathbb{N}_0\times\mathbb{N}_0$, where $\delta_{a,b}$ denotes Kronecker's delta.

By a first-step argument, it is found that the conditional probabilities in the sequence $\{\mathcal{P}(m_1,m_2):m_1,m_2\in\mathbb{N}_0\}$ satisfy a system of linear equations, which is specified as follows:

(i) For initial states $(i,j)\in\mathcal{S}$ with $i\in\{1,...,N-1\}$ and $j\in\{0,...,i\}$,

$$\begin{aligned}
P_{i,j,0}(m_1,m_2) &= \frac{(N-i-1)(\lambda_1+(i-j)\beta_1)}{q_{(i,j)}}P_{i+1,j,0}(m_1,m_2)\\
&\quad+(1-\delta_{0,m_1})\frac{\lambda_1+(i-j)\beta_1}{q_{(i,j)}}P_{i+1,j,1}(m_1-1,m_2)\\
&\quad+\frac{(N-i-1)(\lambda_2+j\beta_2)}{q_{(i,j)}}P_{i+1,j+1,0}(m_1,m_2)\\
&\quad+(1-\delta_{0,m_2})\frac{\lambda_2+j\beta_2}{q_{(i,j)}}P_{i+1,j+1,2}(m_1,m_2-1)\\
&\quad+\frac{(i-j)\gamma_1}{q_{(i,j)}}\left(\delta_{1,i}\delta_{(0,0),(m_1,m_2)}+(1-\delta_{1,i})P_{i-1,j,0}(m_1,m_2)\right)\\
&\quad+\frac{j\gamma_2}{q_{(i,j)}}\left(\delta_{1,i}\delta_{(0,0),(m_1,m_2)}+(1-\delta_{1,i})P_{i-1,j-1,0}(m_1,m_2)\right),
\end{aligned}\tag{2}$$

for integers $m_1,m_2\in\mathbb{N}_0$.

(ii) For initial states $(i,j)\in\mathcal{S}$ with $i\in\{1,...,N\}$ and $j\in\{0,...,i-1\}$,

$$\begin{aligned}
P_{i,j,1}(m_1,m_2) &= \frac{(N-i)(\lambda_1+(i-j)\beta_1)}{q_{(i,j)}}P_{i+1,j,1}(m_1,m_2)\\
&\quad+\frac{(N-i)(\lambda_2+j\beta_2)}{q_{(i,j)}}P_{i+1,j+1,1}(m_1,m_2)
\end{aligned}$$

$$
\begin{aligned}
&+\frac{(i-j-1)\gamma_1}{q_{(i,j)}}P_{i-1,j,1}(m_1,m_2)\\
&+\frac{\gamma_1}{q_{(i,j)}}\left(\delta_{1,i}\delta_{(0,0),(m_1,m_2)}+(1-\delta_{1,i})P_{i-1,j,0}(m_1,m_2)\right)\\
&+\frac{j\gamma_2}{q_{(i,j)}}P_{i-1,j-1,1}(m_1,m_2), \qquad (3)
\end{aligned}
$$

for integers $m_1, m_2 \in \mathbb{N}_0$.

(iii) For initial states $(i,j) \in \mathcal{S}$ with $i \in \{1,...,N\}$ and $j \in \{1,...,i\}$,

$$
\begin{aligned}
P_{i,j,2}(m_1,m_2) \;=\; & \frac{(N-i)(\lambda_1+(i-j)\beta_1)}{q_{(i,j)}}P_{i+1,j,2}(m_1,m_2)\\
&+\frac{(N-i)(\lambda_2+j\beta_2)}{q_{(i,j)}}P_{i+1,j+1,2}(m_1,m_2)\\
&+\frac{(i-j)\gamma_1}{q_{(i,j)}}P_{i-1,j,2}(m_1,m_2)+\frac{(j-1)\gamma_2}{q_{(i,j)}}P_{i-1,j-1,2}(m_1,m_2)\\
&+\frac{\gamma_2}{q_{(i,j)}}\left(\delta_{1,i}\delta_{(0,0),(m_1,m_2)}+(1-\delta_{1,i})P_{i-1,j-1,0}(m_1,m_2)\right), \qquad (4)
\end{aligned}
$$

for integers $m_1, m_2 \in \mathbb{N}_0$.

In solving (2)-(4), it is worth noting that, for a fixed pair $(m_1,m_2) \in \mathbb{N}_0 \times \mathbb{N}_0$, the numerical computation of the conditional probabilities $P_{i,j,k}(m_1,m_2)$, for $k \in \{0,1,2\}$ and initial states (i,j) with $i \in \{1,...,N-\delta_{0,k}\}$ and $j \in \{\delta_{2,k},...,i-\delta_{1,k}\}$, shall require the previous computation of probabilities $P_{i',j',k'}(n_1,n_2)$ for integers $n_1 \in \{0,...,m_1\}$ and $n_2 \in \{0,...,m_2\}$, suitably selected states (i',j') and integers $k' \in \{0,1,2\}$.

To be concrete, we fix the pair $(m_1,m_2) \in \mathbb{N}_0 \times \mathbb{N}_0$ and proceed in $1+m$ phases with $m = \min\{m_1,m_2\}$. During the first phase, we first evaluate the probabilities $P_{i,j,k}(0,0) \in \mathcal{P}(0,0)$, and then compute probabilities in the *neighboring* families $\mathcal{P}(m_1',0)$ and $\mathcal{P}(0,m_2')$ moving up from $m_1'=1$ and $m_2'=1$ towards the integers m_1 and m_2, respectively; see Figure 2. In the $(1+n)$th phase with $n \in \{1,...,m\}$, we first derive values of $P_{i,j,k}(n,n)$ in $\mathcal{P}(n,n)$, and then evaluate probabilities in the neighboring families $\mathcal{P}(m_1',n)$ and $\mathcal{P}(n,m_2')$ with integers $m_1' \in \{n+1,...,m_1\}$ and $m_2' \in \{n+1,...,m_2\}$, by using previously

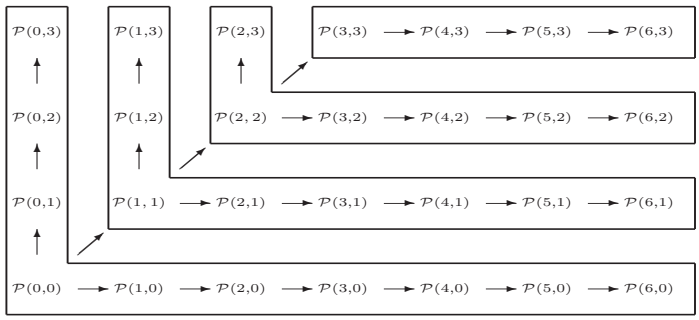

Figure 2: Diagram of iterations yielding Algorithm B (Appendix) for computing conditional probabilities $P_{i,j,k}(m_1, m_2) \in \mathcal{P}(m_1, m_2)$, in the special case $(m_1, m_2) = (6, 3)$.

computed probabilities $P_{i',j',k'}(n_1', n_2') \in \mathcal{P}(n-1, n-1) \cup \cup_{m'=n}^{m_2} \mathcal{P}(n-1, m') \cup \cup_{m'=n}^{m_1} \mathcal{P}(m', n-1)$.

The above iterative scheme can be translated into Algorithms A-B (Appendix). Specifically, Algorithm B is a general-purpose scheme for computing the conditional probabilities $P_{i,j,k}(m_1, m_2) \in \mathcal{P}(m_1, m_2)$, for $(m_1, m_2) \in \mathbb{N}_0 \times \mathbb{N}_0$, from previously computed probabilities $P_{i',j',k'}(n_1, n_2)$ in the family $\mathcal{P}(n, n)$ with $n = \min\{n_1, n_2\}$, and its neighboring families $\mathcal{P}(m_1', n)$ and $\mathcal{P}(n, m_2')$, for integers $m_1' \in \{n+1, ..., m_1\}$ and $m_2' \in \{n+1, ..., m_2\}$, by progressively increasing $n \in \{0, ..., m\}$ with $m = \min\{m_1, m_2\}$. For each fixed pair (m_1', m_2') with $m_1' \in \{n, ..., m_1\}$ and $m_2' \in \{n, ..., m_2\}$, Algorithm A is nested inside Algorithm B and allows us to iteratively compute the conditional probabilities $P_{i,j,0}(m_1', m_2')$, for states (i, j) with $j \in \{0, ..., i\}$, by increasing $i \in \{1, ..., N-1\}$; in a similar manner, the conditional probabilities $P_{i,j,k}(m_1', m_2')$ with $k \in \{1, 2\}$ are then derived from those previously computed values $P_{i,j,0}(m_1', m_2')$. For further details on Algorithms A-B, see Appendix.

4. Numerical experiments and discussion

This section is devoted to numerical experiments to implement the analytical results we obtained in Section 3 as well as to provide evidences that these results are likely to hold in realistic situations. Specifically, experiments in Figures 3-6

are related to the compartmental model of Lipsitch et al. [21], which addresses antibiotic resistance in hospitals; for related work, see the papers by Cen et al. [12], and Gómez-Corral and López-García [17, Section 3.3].

For convenience, we first describe the deterministic model of Lipsitch et al. [21], and then present its stochastic counterpart in terms of the two-strain SIS-model with partial cross-immunity of Sections 2-3.

4.1. The deterministic model of Lipsitch et al. [21]

Lipsitch et al. [21] study a deterministic model for the spread of two bacterial strains among patients of a hospital ward, under the assumption that the infection by one bacterial strain provides immunity against the other during the infectious period of each patient, but they become again susceptible to either bacterial strain after recovering. Because antibiotics are usually used in hospitals to control nosocomial transmission of bacteria, Lipsitch et al. [21] assume that patients in the hospital ward are routinely provided two antimicrobial agents, called *antibiotic A* and *antibiotic B*, regardless of these patients being colonized or not with bacteria. Antibiotic A is effective only against sensitive bacteria, whereas resistance to antibiotic B is not present in the bacteria. This means that patients may carry strains of the bacteria that are either sensitive or resistant to antibiotic A, or they may be free of bacteria. Treatment with antibiotic A, which occurs at rate τ_A per day, clears carriage of sensitive bacteria; and treatment with antibiotic B, which occurs at rate τ_B per day, clears carriage of either sensitive or resistant bacteria. Moreover, spontaneous clearance of sensitive and resistant bacteria occurs at a rate γ_0 per day.

Patients who are free of bacteria become colonized with sensitive bacteria at a rate proportional to the number of patients colonized with sensitive bacteria and at a rate β per day, and the colonization with resistant bacteria occurs at a rate $(1-c)\beta$ per day, where $c \in (0,1)$ amounts to the fitness cost of resistance to antibiotic A. In epidemiological research, the fitness cost is commonly expressed in terms of reduced competitive ability or virulence, and translated here into the reduced growth rate $(1-c)\beta$ for the resistant bacteria since $c \in (0,1)$; note

that, for more general purposes, the value $1-c$ should be replaced by c' with $c' > 0$. Unlike Lipsitch et al. [21], it is assumed here that infections by sensitive and resistant bacteria not directly caused by infectious contacts occur at rates $\lambda_{AS} \geq 0$ and $\lambda_{AR} \geq 0$ per day, respectively. It is also assumed in [21] that patients are admitted by and discharged from the hospital ward at a constant rate μ per day, in such a way that the average duration of stay in the hospital ward is μ^{-1} days; in our examples, we focus on the case where patients who are discharged from the hospital ward are immediately replaced by newly admitted patients, who are assumed to be free of bacteria.

From the above, Lipsitch et al. [21, page 1939] derive a set of ordinary differential equations for the fractions $f_{AS}(t)$ and $f_{AR}(t)$ of patients who are colonized with either sensitive bacteria or resistant bacteria, respectively, and the fraction $f_F(t)$ of patients who are free of bacteria at time t. Since $f_{AS}(t) + f_{AR}(t) + f_F(t) = 1$ at any time t, it is summarized by the pair

$$\begin{aligned}
\frac{df_{AS}(t)}{dt} &= (\lambda_{AS} + \beta f_{AS}(t))\,(1 - f_{AS}(t) - f_{AR}(t)) - (\tau_A + \tau_B + \gamma + \mu)\,f_{AS}(t), \\
\frac{df_{AR}(t)}{dt} &= (\lambda_{AR} + (1-c)\beta f_{AR}(t))\,(1 - f_{AS}(t) - f_{AR}(t)) - (\tau_B + \gamma + \mu)\,f_{AR}(t),
\end{aligned}$$

of differential equations, and is thus a particular instance of a multi-type SIS-model; see [17, Sections 3.2-3.3] and [27].

4.2. The stochastic version

Under the assumption of exponentially distributed infectious, clearance and discharge periods, and Poisson processes governing infectious contacts and infections not directly caused by infectious contacts, the dynamics of the deterministic model in [21] can be replaced by the Markov chain model $(I_1(t)+I_2(t), I_2(t))$ with *internal* infectious rates $\beta_1 = N^{-1}\beta$ and $\beta_2 = N^{-1}(1-c)\beta$, *exogeneous* infection rates $\lambda_1 = \lambda_{AS}$ and $\lambda_2 = \lambda_{AR}$, and recovery rates $\gamma_1 = \gamma_0 + \tau_A + \tau_B + \mu$ and $\gamma_2 = \gamma_0 + \tau_B + \mu$, where N is the number of beds in the hospital ward; in the terminology of Sections 2-3, infections of type 1 and of type 2 amount to colonization with antibiotic-sensitive (AS) bacteria and with antibiotic-resistant (AR) bacteria, respectively. Observe that, unlike the paper [21] where the model

Description and parameters		Values
Number of beds	N	20 beds
Fitness cost	c	$\{0.25, 0.5, 0.75\}$
Average time for exogenous AS bacterial infection	λ_{AS}^{-1}	$(N^{-1}0.1)^{-1}$ days
Average time for exogenous AR bacterial infection	λ_{AR}^{-1}	$(N^{-1}0.1)^{-1}$ days
Average response of antibiotic A	τ_A^{-1}	5 days
Average response of antibiotic B	τ_B^{-1}	$\{7.5, ..., 20\}$ days
Average duration of spontaneous clearance	γ_0^{-1}	30 days
Average duration of stay	μ^{-1}	7 days

Table 1: Model parameters and their values in Figures 3-6, when the average time $\beta^{-1} = 1$ *day* corresponds to the transmission of sensitive bacteria.

is related to fractions, we consider rates $\beta_1 = N^{-1}\beta$ and $\beta_2 = N^{-1}(1-c)\beta$ instead of β and $(1-c)\beta$, since the random variables in the Markov chain model $(I_1(t) + I_2(t), I_2(t))$ amount to numbers of colonized patients.

We are particularly interested in the numbers M_1 and M_2 of infections –by the AS and AR bacterial strains, respectively– suffered by the patients who are one after another accommodated in a *focal* bed during an outbreak, in the case of initial numbers $(I_1(0), I_2(0)) = (1, 1)$ of infective individuals. It is also assumed that initially a patient who is free of bacteria (i.e., $k = 0$) is accommodated in the focal bed, and therefore two non-focal beds initially accommodate patients colonized with sensitive and resistant bacteria; we recall that discharged patients are replaced by newly admitted patients who initially are not colonized by bacteria. It should be noted that M_1 and M_2 are cumulative numbers and, because during the outbreak a random number R of patients may be likely accommodated in the focal bed, they are not necessarily linked to a single patient. Regarding to one of those R patients, the patient shall contribute to the vector (M_1, M_2) with numbers (m_1^*, m_2^*) of infections by sensitive and resistant bacteria, where $(m_1^*, m_2^*) = (0, 0)$ if the patient is not colonized with bacteria during his/her stay. Similarly, pairs $(m_1^*, m_2^*) \in \mathbb{N}_0 \times \mathbb{N}_0 \setminus \{(0, 0)\}$ are also likely and

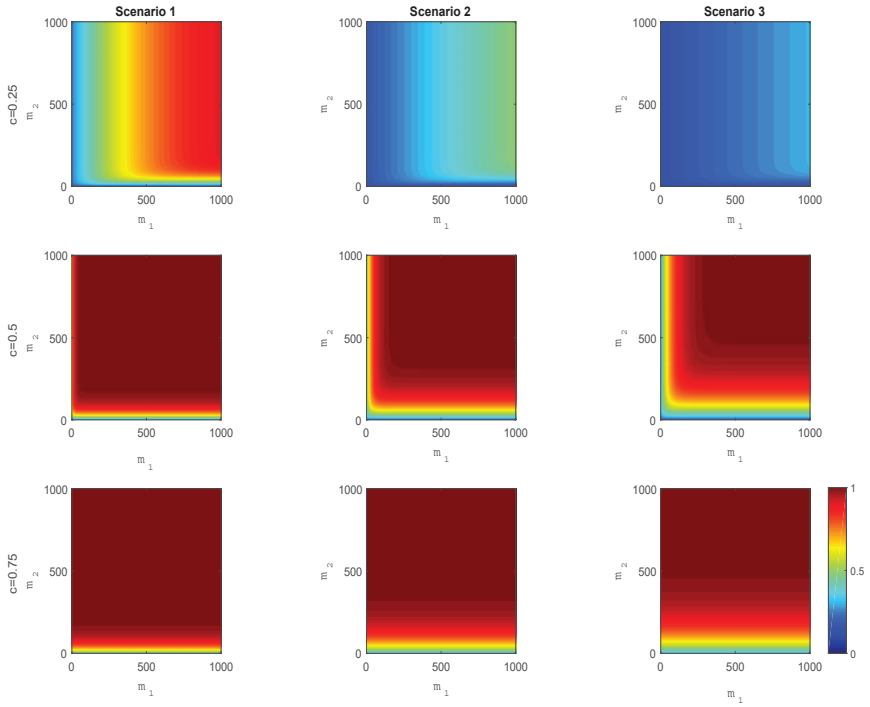

Figure 3: Probability distribution function $F_{2,1,0}(m_1, m_2)$ of (M_1, M_2) versus c, in scenarios 1-3.

are associated with a single colonization and multiple colonizations with either sensitive bacteria or resistant bacteria during the stay of the patient; more concretely, pairs $(m_1^*, m_2^*) \in \{(1,0),(0,1)\}$ amount to a single colonization, and multiple colonizations are related to pairs (m_1^*, m_2^*) with $m_1^*, m_2^* \in \mathbb{N}$.

In Figures 3-6, numerical examples are presented to illustrate the dynamics of both bacterial strains in terms of M_1 and M_2 in three scenarios with $N = 20$ *beds*, $\beta^{-1} = 1$ *day*, $\tau_A^{-1} = 5$ *days*, $\gamma_0^{-1} = 30$ *days* and $\mu^{-1} = 7$ *days*. Scenarios 1, 2 and 3 are specifically defined according to the effectiveness of antibiotic B from average responses $\tau_B^{-1} = 10$ *days*, 15 *days* and 20 *days*, respectively; note that these parameters (Table 1) come from Lipsitch et al. [21].

In Figures 3-4, the interest is in the joint probability distribution function

of (M_1, M_2), which is evaluated (Algorithms A-B) as

$$F_{2,1,0}(m_1, m_2) \quad = \quad \sum_{m_1'=0}^{m_1} \sum_{m_2'=0}^{m_2} P_{2,1,0}(m_1', m_2'),$$

for integers $(m_1, m_2) \in \mathbb{N}_0 \times \mathbb{N}_0$. Figure 3 is a preliminary description of the numbers (M_1, M_2) of infections in terms of $F_{2,1,0}(m_1, m_2)$, for integers $m_1, m_2 \in \{0, ..., 1000\}$ and values $c \in \{0.25, 0.5, 0.75\}$, in scenarios 1-3. Roughly speaking, it is seen that the probability law of (M_1, M_2) is expected to be more concentrated on small numbers (m_1, m_2) of infections when the effectiveness of antibiotic B increases –equivalently, with decreasing values of τ_B^{-1}–, regardless of the fitness cost c. More concretely, smaller values of the fitness cost turn the probability law of (M_1, M_2) into a more sparse law when the effectiveness of antibiotic B decreases; in particular, the selection $c = 0.25$ in scenario 1 yields the law of (M_1, M_2) with the heaviest tail in our experiments.

In Figure 4, the focus is on sets $\{(m_1, m_2) : m_1, m_2 \in \{0, ..., K_q\}\}$, where the $(100q)$th bivariate percentiles[1] K_q, for $q = 0.9$, of (M_1, M_2) are given by 1009, 161 and 229 in scenarios 1 (with $c = 0.25$), 2 ($c = 0.5$) and 3 ($c = 0.75$), respectively. Figure 5 is a basic description of the probability law of the numbers (M_1, M_2) of colonizations in terms of the quartiles $K_{0.25}$, $K_{0.5}$ and $K_{0.75}$ in scenarios 1 (with $c = 0.25$), 2 ($c = 0.5$) and 3 ($c = 0.75$), as a function of the effectiveness of antibiotic B; for illustrative purposes, we use the range $K_q \in \{0, ..., 1000\}$ in the vertical axis for scenario 1 (with $c = 0.25$), since the magnitudes of K_q for $q \in \{0.5, 0.75\}$ in scenario 1 ($c = 0.25$) are not comparable with those in scenarios 2 ($c = 0.5$) and 3 ($c = 0.75$). It is clearly seen that the number M_2 (respectively, M_1) of colonizations with resistent bacteria (respectively, sensitive bacteria) is expected to be larger than its sensitive counterpart M_1 (respectively, resistant counterpart M_2) when the effectiveness of antibiotic B increases (respectively, decreases) and the fitness cost c decreases (respectively, increases), whereas intermediate values of c and τ_B^{-1} appear to result in

[1] For $q \in (0, 1)$, the $(100q)$th *bivariate* percentile K_q of (M_1, M_2) is defined here as the smallest integer K verifying $F_{2,1,0}(K-1, K-1) \leq q < F_{2,1,0}(K, K)$.

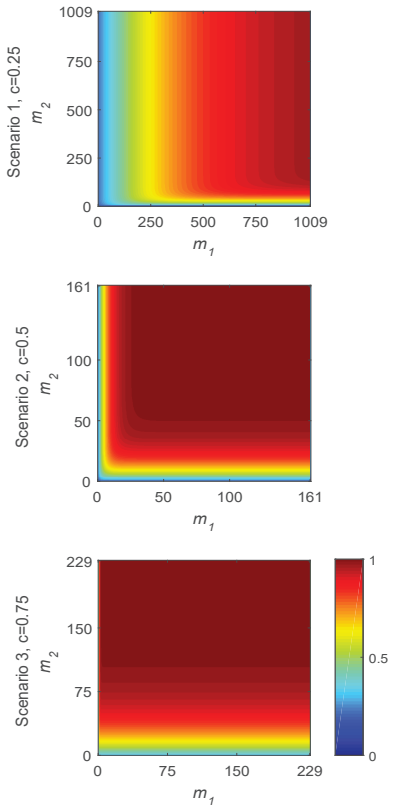

Figure 4: Probability distribution function $F_{2,1,0}(m_1, m_2)$ of (M_1, M_2) for pairs (m_1, m_2) with $m_1, m_2 \in \{0, 1, ..., K_{0.9}\}$, in scenarios 1 (with $c = 0.25$), 2 ($c = 0.5$) and 3 ($c = 0.75$).

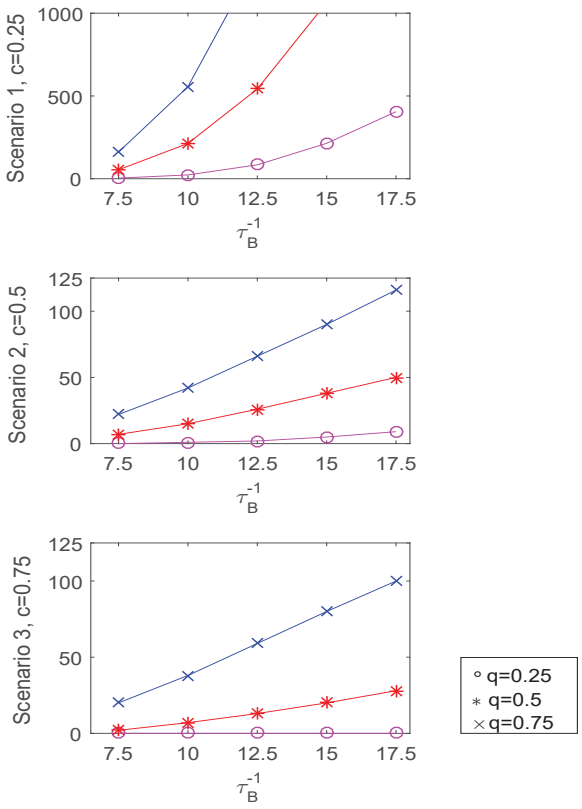

Figure 5: Values of the $(100q)$th percentiles K_q, for $q \in \{0.25, 0.5, 0.75\}$, versus τ_B^{-1}, in scenarios 1 (with $c = 0.25$), 2 ($c = 0.5$) and 3 ($c = 0.75$).

balanced outcomes of the numbers M_1 and M_2 of colonizations with sensitive and resistant bacteria.

The above assertion is clearly corroborated by Figure 6 and Table 2, where the marginal distributions of the numbers M_1 and M_2 of sensitive and resistant infections are plotted in terms of the *restricted* mass functions

$$P_{2,1,0}^{(k)}(m;q) \quad = \quad P(M_k = m | (M_1, M_2) \leq (K_q, K_q)), \quad m \in \{0, ..., K_q\},$$

for $k \in \{1, 2\}$; from Algorithms A-B, the conditional probabilities $P(M_k = m|(M_1, M_2) \leq (K_q, K_q))$ are evaluated as $(F_{2,1,0}(K_q, K_q))^{-1} \sum_{m_2=0}^{K_q} P_{2,1,0}(m, m_2)$ if $k = 1$, and $(F_{2,1,0}(K_q, K_q))^{-1} \sum_{m_1=0}^{K_q} P_{2,1,0}(m_1, m)$ if $k = 2$. The parameters

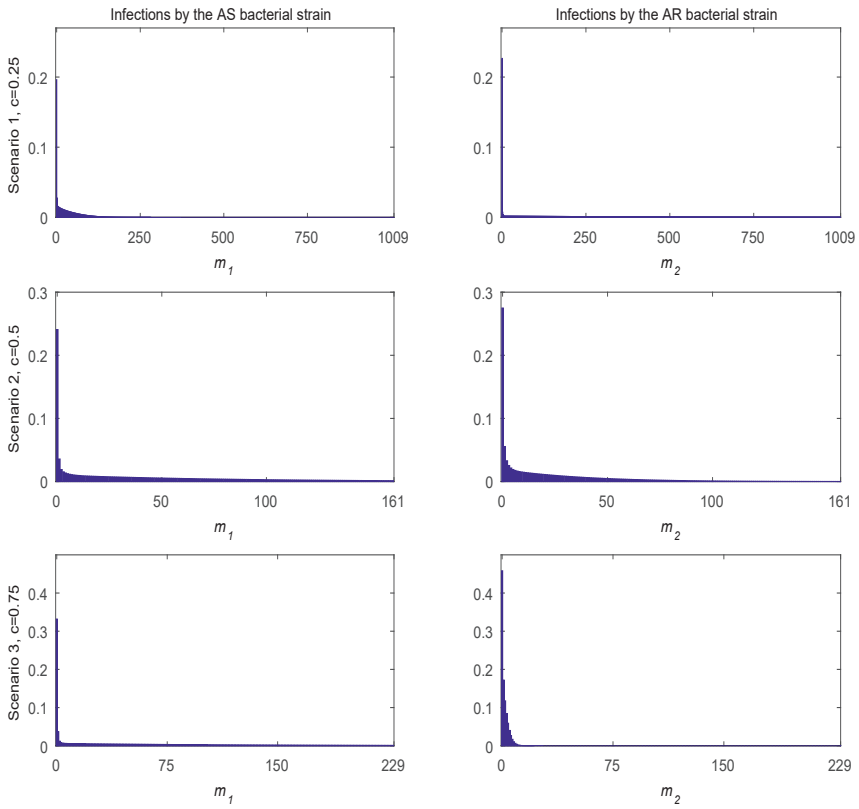

Figure 6: Marginal distributions of M_1 and M_2 in terms of the conditional mass functions $\{P^{(1)}_{2,1,0}(m_1;0.9) : m_1 \in \{0,1,...,K_{0.9}\}\}$ and $\{P^{(2)}_{2,1,0}(m_2;0.9) : m_2 \in \{0,1,...,K_{0.9}\}\}$, respectively, in scenarios 1 (with $c = 0.25$), 2 ($c = 0.5$) and 3 ($c = 0.75$).

Scenario, fitness cost	$E_{K_q}[M_1]$	$E_{K_q}[M_2]$
Scenario 1, $c = 0.25$	34.47374	255.75099
Scenario 2, $c = 0.5$	39.21072	21.30988
Scenario 3, $c = 0.75$	50.73162	1.61253

Table 2: Expectations $E_{K_q}[M_k] = \sum_{m=1}^{K_q} mP^{(k)}_{2,1,0}(m;q)$, for $k \in \{1,2\}$ and $q = 0.9$, in scenarios 1 (with $c = 0.25$), 2 ($c = 0.5$) and 3 ($c = 0.75$).

fixed in Figure 6 have the same values as those in Figure 5, so that the integers 1009, 161 and 229 in the horizontal axis correspond to the percentiles $K_{0.9}$ in scenarios 1 (with $c = 0.25$), 2 ($c = 0.5$) and 3 ($c = 0.75$), respectively.

5. Conclusions

We have presented a stochastic framework for analyzing the spread of two competing pathogen strains in terms of the joint distribution of the numbers M_1 and M_2 of type-1 and type-2 infections suffered by a concrete individual during an outbreak of the disease. The focus has been on the two-strain SIS-model with partial cross-immunity, where neither coinfection nor mutation are possible, and it is assumed that infective individuals become susceptible individuals to both strains of bacteria after recovering. This work is part of an ongoing study on how heterogeneous infectiousness and/or susceptibility may influence the dynamics of epidemic models, including SIS-models with heterogeneous contacts [14], multi-type SIS-models [17], and SIR-models with two-strains and total cross-immunity [4].

Our approach is based on an algorithmic solution, which exploits the specific matrix structure of the underlying infinitesimal generator, from which the joint mass function of (M_1, M_2) is iteratively derived under the assumption that the initial state of the focal individual –who is either free of bacteria, or infective of type 1 or of type 2– is known. Because the most intensive computational effort in Algorithms A-B (Appendix) is related to the inversion and product of matrices, it can be readily verified that Algorithms A-B have a computational complexity similar to other well-known algorithms for LD-QBD processes, such as the linear level reduction algorithm for the stationary distribution (see Latouche and Ramaswami [20, Section 10.1]) and Algorithms 1.A-2.A of Gómez-Corral and López-García [17, Section 2] for first-passage times and hitting probabilities, among others. Small population sizes N are commonly related to small communities sharing confined spaces as families, nursing homes and intensive care units, among other practically relevant situations where stochastic effects –due

to the random nature of infections– can generate significant deviations from the deterministic solution. From a theoretical perspective, the Markov chain model in Sections 2-3 and its application in Section 4 remain valid regardless of the population size N, but at the expense of limited computational tractability. For problems with a large size N, an alternative approach is the theory of density dependent population processes; see e.g. the monograph by Ethier and Kurtz [15, Section 11.2], where asymptotics for a variety of examples, including the numbers of infective and susceptible individuals in the SIS and SIR epidemic models, are derived in terms of a law of large numbers and the central limit theorem.

In the context of nosocomial pathogens, we illustrate in Section 4 the approach by describing the spread of sensitive and resistant bacteria among patients within a hospital ward. Unlike the studies of Cen et al. [12], and Lipsitch et al. [21] where the interest is in deterministic models, we show how Markov chain models can be helpful for understanding the transmission of resistance in hospitals. Our numerical results highlight that the effectiveness of antibiotics is an important but not unique piece of the overall resistance problem, and factors such as the fitness cost also have a strong effect on the numbers of infections.

We stress that our arguments in Section 4 are based upon the observation that the term *focal bed* amounts to *focal individual* in Section 3. Consequently, the random pair (M_1, M_2) is not linked to a single patient in Section 4 and is thought of as a global infection control index to measure the effects of antibiotic use at the population level (population prevalence), instead of the patient level (risk factors). Whilst it is outside the scope of this work, we point out that the analysis of the number R of patients to be accommodated in the focal bed during an outbreak –as well as the contribution to (M_1, M_2) of each patient– is more complex than that presented in Section 3.

It is evident that the assumption of exponentially distributed infectious periods is generally not realistic (see e.g. Lloyd [22]), but does facilitate calculations. We refer the reader to the papers by Keeling and Grenfell [18], and Vergu et al. [28] on the effects of more realistic distributions in epidemic models, among oth-

ers; see also [13, 16], where piecewise-deterministic Markov processes are used in SIR-models with generally distributed infectious periods.

Acknowledgements

The authors thank the editor and two anonymous referees whose comments and suggestions led to improvements in the manuscript. This work is supported by the Ministry of Economy, Industry and Competitiveness (Government of Spain), Project MTM2014-58091-P.

Conflict of interest

There are no conflicts of interest to this work.

Appendix: Algorithmic solution

In deriving the conditional probabilities $P_{i,j,k}(n_1, n_2)$ for $k \in \{0, 1, 2\}$ and a fixed pair (n_1, n_2) with $n_1 \in \{0, ..., m_1\}$ and $n_2 \in \{0, ..., m_2\}$, it is observed that the column vectors $\mathbf{p}_{i,\cdot,0}(n_1, n_2)$, for $i \in \{1, ..., N-1\}$, with $(1+j)$th entry $P_{i,j,0}(n_1, n_2)$, for $j \in \{0, ..., i\}$, satisfy a system of linear equations with structured form

$$\begin{pmatrix} -\mathbf{B}_1 & -\mathbf{C}_1 & & & \\ -\mathbf{A}_2 & -\mathbf{B}_2 & -\mathbf{C}_2 & & \\ & \ddots & \ddots & \ddots & \\ & & -\mathbf{A}_{J-1} & -\mathbf{B}_{J-1} & -\mathbf{C}_{J-1} \\ & & & -\mathbf{A}_J & -\mathbf{B}_J \end{pmatrix} \begin{pmatrix} \mathbf{u}_1 \\ \mathbf{u}_2 \\ \vdots \\ \mathbf{u}_{J-1} \\ \mathbf{u}_J \end{pmatrix} = \begin{pmatrix} \mathbf{v}_1 \\ \mathbf{v}_2 \\ \vdots \\ \mathbf{v}_{J-1} \\ \mathbf{v}_J \end{pmatrix}, \tag{5}$$

where $J = N - 1$ and the column vectors $\mathbf{v}_i$ are specified as follows:

(i) For the pair $(n_1, n_2) = (0, 0)$, the vector $\mathbf{v}_i$ has the form $\mathbf{v}_i = (\gamma_1, \gamma_2)^T$ if $i = 1$, and $\mathbf{0}_{i+1}$ if $i \in \{2, ..., N-1\}$, where $\mathbf{0}_a$ is the null vector of order a and ^{T} denotes transposition.

(ii) For pairs $(n_1, n_2) \neq (0,0)$, the vector $\mathbf{v}_i$ is given by $\mathbf{v}_i = (1-\delta_{0,n_1})\mathrm{diag}(\lambda_1 + i\beta_1, \lambda_1+(i-1)\beta_1, ..., \lambda_1+\beta_1, \lambda_1)\mathbf{p}_{i+1,\cdot,1}(n_1-1, n_2)+(1-\delta_{0,n_2})\mathrm{diag}(\lambda_2, \lambda_2+\beta_2, ..., \lambda_2+(i-1)\beta_2, \lambda_2+i\beta_2)\mathbf{p}_{i+1,\cdot,2}(n_1, n_2-1)$, for $i \in \{1, ..., N-1\}$.

From (2)-(4), it is readily seen that the matrices $\mathbf{A}_i$, $\mathbf{B}_i$ and $\mathbf{C}_i$ in Eq. (5) have non-null entries $(\mathbf{A}_i)_{1+j,1+j'} = (i-j)\gamma_1$ if $j' = j$, and $j\gamma_2$ if $j' = j-1$, for $j \in \{0, ..., i\}$ and $j' \in \{0, ..., i-1\}$; $(\mathbf{B}_i)_{1+j,1+j'} = -q_{(i,j)}$ if $j' = j$, for $j \in \{0, ..., i\}$; and $(\mathbf{C}_i)_{1+j,1+j'} = (N-i-1)(\lambda_1 + (i-j)\beta_1)$ if $j' = j$, and $(N-i-1)(\lambda_2 + j\beta_2)$ if $j' = j+1$, for $j \in \{0, ..., i\}$ and $j' \in \{0, ..., i+1\}$.

With respect to the conditional probabilities $P_{i,j,k}(n_1, n_2)$ with $k \in \{1, 2\}$, it is seen that the column vectors $\mathbf{p}_{i,\cdot,k}(n_1, n_2)$, for $i \in \{1, ..., N\}$, with $(1+j)$th entries $P_{i,j,k}(n_1, n_2)$, for $j \in \{\delta_{2,k}, ..., i-\delta_{1,k}\}$, also verify (5) with the integer $J = N$ and the column vectors $\mathbf{v}_i = \gamma_k \delta_{(0,0),(n_1,n_2)}$ if $i = 1$, and $\gamma_k \mathbf{p}_{i-1,\cdot,0}(n_1, n_2)$ if $i \in \{2, ..., N\}$. The non-null entries of $\mathbf{A}_i$, $\mathbf{B}_i$ and $\mathbf{C}_i$ in the cases $k \in \{1, 2\}$ can be expressed as $(\mathbf{A}_i)_{1+j,1+j'} = (i-j-1)\gamma_1$ if $j' = j$, and $j\gamma_2$ if $j' = j-1$, for $j \in \{0, ..., i-1\}$ and $j' \in \{0, ..., i-2\}$; $(\mathbf{B}_i)_{1+j,1+j'} = -q_{(i,\delta_{2,k}+j)}$ if $j' = j$, for $j \in \{0, ..., i-1\}$; and $(\mathbf{C}_i)_{1+j,1+j'} = (N-i)(\lambda_1 + (i-j-\delta_{2,k})\beta_1)$ if $j' = j$, and $(N-i)(\lambda_2 + (j+\delta_{2,k})\beta_2)$ if $j' = j+1$, for $j \in \{0, ..., i-1\}$ and $j' \in \{0, ...i\}$.

This results in Algorithm A, which allows us to compute the column vectors $\mathbf{p}_{i,\cdot,0}(n_1, n_2)$ by solving (5) for the unknowns $\mathbf{u}_i$, for $i \in \{1, ..., J\}$ with $J = N-1$ and the above specifications for the case $k = 0$; i.e., the vectors $\mathbf{v}_i$ in Algorithm A are specified in terms of the previously computed vectors $\mathbf{p}_{i+1,\cdot,1}(n_1-1, n_2)$ and $\mathbf{p}_{i+1,\cdot,2}(n_1, n_2-1)$ in the case $(n_1, n_2) \neq (0,0)$. Once $\{\mathbf{p}_{i,\cdot,0}(n_1, n_2) : i \in \{0, ..., N-1\}\}$ are evaluated, we may then derive the column vectors $\{\mathbf{p}_{i,\cdot,k}(n_1, n_2) : i \in \{1, ..., N\}\}$ with $k \in \{1, 2\}$ by specifying the vectors $\mathbf{v}_i = \gamma_k \delta_{(0,0),(n_1,n_2)}$ if $i = 1$, and $\gamma_k \mathbf{p}_{i-1,\cdot,0}(n_1, n_2)$ if $i \in \{2, ..., N\}$.

Algorithm A *Computation of the column vectors* $\mathbf{u}_i$*, for* $i \in \{0, ..., J\}$*, by using block-Gaussian elimination.*

Step 1: $i := 0$;

while $i < J$,

$i := i + 1$;

$\mathbf{W}_i := \mathbf{B}_{i,i} + (1 - \delta_{1,i})\mathbf{A}_i\mathbf{V}_i$;

$\mathbf{w}_i := -\mathbf{W}_i^{-1}(\mathbf{v}_i + (1 - \delta_{1,i})\mathbf{A}_i\mathbf{w}_{i-1})$;

if $i < J$, then

$\mathbf{V}_i := -\mathbf{W}_i^{-1}\mathbf{C}_i$.

Step 2: While $i > 1$,

$\mathbf{u}_i := \mathbf{w}_i + (1 - \delta_{i,J})\mathbf{u}_{i+1}$;

$i := i - 1$.

For a fixed pair $(m_1, m_2) \in \mathbb{N}_0 \times \mathbb{N}_0$, Algorithm B allows us to progressively compute the conditional probabilities $P_{i,j,k}(n_1, n_2)$ in the family $\mathcal{P}(n, n)$ with $n = \min\{n_1, n_2\}$, and its neighboring counterparts $\mathcal{P}(m_1', n)$ and $\mathcal{P}(n, m_2')$, for integers $m_1' \in \{n + 1, ..., m_1\}$ and $m_2' \in \{n + 1, ..., m_2\}$, by appropriately increasing (Figure 2) the pair (n_1, n_2).

Algorithm B *Computation of the vectors* $\{\mathbf{p}_{i,\cdot,k}(m_1, m_2) : i \in \{1, ..., N - \delta_{0,k}\}, k \in \{0, 1, 2\}\}$*, for a fixed pair* $(m_1, m_2) \in \mathbb{N}_0 \times \mathbb{N}_0$.

$m := \min\{m_1, m_2\}$;

$n := 0$;

while $n \leq m$,

$m_1' := n$;

$m_2' := n + 1$;

while $m_1' \leq m_1$,

$k := 0$;

while $k \leq 2$,

$\{\mathbf{p}_{i,\cdot,k}(m_1', n) : i \in \{1, ..., N - \delta_{0,k}\}\} \leftarrow$ from Algorithm A;

$k := k + 1$;

while $m_2' \leq m_2$,

$k := 0$;

while $k \leq 2$,

$\{\mathbf{p}_{i,\cdot,k}(n, m_2') : i \in \{1, ..., N - \delta_{0,k}\}\} \leftarrow$ from Algorithm A;

$k := k + 1$;

$n := n + 1$.

References

[1] Ackleh AS, Allen LJS (2005) Competitive exclusion in SIS and SIR epidemic models with total cross immunity and density-dependent host mortality. *Discrete and Continuous Dynamical Systems B*, **5,** 175–188.

[2] Allen LJS, Langlais M, Phillips CJ (2003) The dynamics of two viral infections in a single host population with applications to hantavirus. *Mathematical Biosciences*, **186,** 191–217.

[3] Allen LJS, Kirupaharan N (2005) Asymptotic dynamics of deterministic and stochastic epidemic models with multiple pathogens. *International Journal of Numerical Analysis and Modelling*, **2,** 329–344.

[4] Amador J, Armesto D, Gómez-Corral A (2019) Extreme values in SIR epidemic models with two strains and cross-immunity. *Mathematical Biosciences and Engineering*, **16,** 1992-2022.

[5] Ball F, Britton T (2005) An epidemic model with exposure-dependent severities. *Journal of Applied Probability*, **42,** 932-949.

[6] Ball F, Becker NG (2006) Control of transmission with two types of infection. *Mathematical Biosciences*, **200,** 170–187.

[7] Ball F, Britton T (2007) An epidemic model with infector-dependent severity. *Advances in Applied Probability*, **39,** 949–972.

[8] Bhattacharyya S, Gesteland PH, Korgenski K, Bjørnstad ON, Adler FR (2015) Cross-immunity between strains esplains the dynamical pattern of paramyxoviruses. *Proceedings of the National Academy of Sciences*, **112,** 13396–13400.

[9] Bhunu CP, Garira W, Magombedze G (2009) Mathematical analysis of a two strain HIV/AIDS model with antiretroviral treatment. *Acta Biotheorica*, **57,** 361–381.

[10] Boëlle PY, Thomas G (2016) Resistance to antibiotics: limit theorems for a stochastic SIS model structured by level of resistance. *Journal of Mathematical Biology*, **73,** 1353–1378.

[11] Castillo-Chávez C, Song B (2004) Dynamical models of tuberculosis and their applications. *Mathematical Biosciences in Engineering*, **1,** 361–404.

[12] Cen X, Feng Z, Zheng Y, Zhao Y (2017) Bifurcation analysis and global dynamics of a mathematical model of antibiotic resistance in hosptials. *Journal of Mathematical Biology*, **75,** 1463-1485.

[13] Clancy D (2014) SIR epidemic models with general infectious period distribution. *Statistics and Probability Letters*, **85,** 1-5.

[14] Economou A, Gómez-Corral A, López-García M (2015) A stochastic SIS epidemic model with heterogeneous contacts. *Physica A*, **421,** 78–97.

[15] Ethier SN, Kurtz TG (1986) *Markov Processes: Characterization and Convergence*, John Wiley and Sons, New York.

[16] Gómez-Corral A, López-García M (2017) On SIR epidemic models with generally distributed infectious periods: Number of secondary cases and probability of infection. *International Journal of Biomathematics*, **10,** 1750024 (13 pages).

[17] Gómez-Corral A, López-García M (2018) Perturbation analysis in finite LD-QBD processes and applications to epidemic models. *Numerical Linear Algebra with Applications*, **25,** 2160 (22 pages).

[18] Keeling MJ, Grenfell BT (1998) Effect of variability in infection period on the persistence and spatial spread of infectious diseases. *Mathematical Biosciences*, **147,** 207-226.

[19] Kendall WS, Saunders IW (1983) Epidemics in competition II: The general epidemic. *Journal of the Royal Statististical Society B*, **45,** 238–244.

[20] Latouche G, Ramaswami V (1999) *Introduction to Matrix Analytic Methods in Stochastic Modeling*, ASA-SIAM, Philadelphia.

[21] Lipsitch M, Bergstrom CT, Levin BR (2000) The epidemiology of antibiotic resistance in hospitals: Paradoxes and prescriptions. *Proceedings of the National Academy of Sciences*, **97,** 1938–1943.

[22] Lloyd AL (2001) Realistic distributions of infectious periods in epidemic models: Changing patterns of persistence and dynamics. *Theoretical Population Biology*, **60,** 59-71.

[23] Lopes F, Luczak M (2018) Extinction time for the weaker of two competing SIS epidemics. ArXiv:1802.04037v1.

[24] Naresh R, Tripathi A (2005) Modelling and analysis of HIV-TB co-infection in a variable size population. *Mathematical Modelling and Analysis*, **10,** 275–286.

[25] Nuño M, Feng Z, Martcheva M, Castillo-Chávez C (2005) Dynamics of two-strain influenza with isolation and partial cross-immunity. *SIAM Journal of Applied Mathematics*, **65,** 964–982.

[26] Rowthorn R, Walther S (2017) The optimal treatment of an infectious disease with two strains. *Journal of Mathematical Biology*, **74,** 1753–1791.

[27] Saunders IW (1981) Epidemics in competition. *Journal of Mathematical Biology* **11,** 311-318.

[28] Vergu E, Busson H, Ezanno P (2010) Impact of the infection period distribution in the epidemic spread in a metapopulation model. *PLoS ONE*, **5,** e9371 (16 pages).