A Markov chain model to investigate the spread of antibiotic-resistant bacteria in hospitals

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Abstract

This paper proposes a Markov chain model to describe the spread of a single bacterial species in a hospital ward where patients may be free of bacteria or may carry bacterial strains that are either sensitive or resistant to antimicrobial agents. The aim is to determine the probability law of the *exact* reproduction number $\mathcal{R}_{exact,0}$, which is here defined as the random number of secondary infections generated by those patients who are accommodated in a predetermined bed before a patient who is free of bacteria is accommodated in this bed for the first time. Specifically, we decompose the exact reproduction number $\mathcal{R}_{exact,0}$ into two contributions allowing us to distinguish between infections due to the sensitive and the resistant bacterial strains. Our methodology is mainly based on structured Markov chains and the use of related matrix-analytic methods.

Keywords: Epidemic model, Markov chain, quasi-birth-death process, reproduction number

Abbreviations: LD-QBD, level-dependent quasi-birth-death; SI, susceptible-infective; SIS, susceptible-infective-susceptible; SIR, susceptible-infective-removed.

1 Introduction

Nosocomial infections caused by antibiotic (or antimicrobial) resistant bacteria —such as methicillin-resistant *Staphylococcus aureus* (Haaber et al. [26]), multidrug-resistant *Mycobacterium tuberculosis* (Gygli et al. [25]), vancomysin-resistant *Enterococci* (Miller et al. [28]), and multidrug-resistant *Gram-negative bacilli* (Breijyeh et al. [8]), among others— are usually most prevalent in intensive care units and hospital settings where patients are susceptible to the acquisition of carriage, mainly due to high selective antibiotic pressure or frequent opportunities for cross-transmission. Compared to infections caused by antibiotic sensitive bacteria, infections caused by resistant bacteria drastically reduce the probability of successfully treating bacterial infections, prolong hospitalizations, and increase healthcare costs, morbidity and mortality, among other implications; see e.g. D'Agata et al. [15] and references therein. The collaborative paper [29] is a first comprehensive assessment of the global burden of antimicrobial resistance and an evaluation of the availability of data in 2019.

To examine the implications of the emergence and spread of antibiotic resistance, mathematical modelling (Niewiadomska et al. [30]) provides a platform for *in silico* experiments that improve our ability to determine the quantitative effects of the transmission process and potential control measures. Most of the existing models follow a deterministic approach, mostly based on the use of ordinary differential equations, on either within-host (Techitnutsarut and Chamchod [33]) or between-host (Bagkur et al. [7]; D'Agata et al. [14]; Lipsitch et al. [27]) frameworks; for a novel work formulating a two-level population model, we refer the reader to the paper by Webb et al. [34]. An excellent summary on antibiotic-resistance modelling is the review of Spicknall et al. [32], where the peer-reviewed literature on between-host resistance modelling —in particular, papers published from 1993 to 2011— is categorized by classifying each paper's model structure into up to six categories based on the underlying inherent assumptions. In the probabilistic setting, Seigal et al. [31] introduce a transmission model —which uses the negative binomial distribution—, present a statistical hypothesis test that calculates the significance of resistance trends occurring in a hospital, and apply the method to each of sixteen antibiotics in a case study of spectrum β-lactamases samples collected from patients at a community hospital over a 2.5-year period.

In this paper, the aim is to complement the work of Gómez-Corral and López-García [21], which is related to a stochastic version of the deterministic between-host model of Lipsitch et al. [27] for antimicrobial resistance in nosocomial pathogens; in a more general context, see the book of Allen [1] for a comprehensive discussion of results on deterministic epidemic models and their stochastic counterparts. The analysis in [21, Section 3.3] illustrates how to apply a perturbation approach of finite level-dependent quasi-birth-death (LD-QBD) processes to two-strain susceptible-infective (SI) and susceptible-infective-susceptible (SIS) epidemic models. Specifically, the random length of an outbreak, the final size of the epidemic, the peak of infection and the state of the population at an arbitrary time in these epidemic models are analyzed in [21] as first-passage times, hitting probabilities, extreme values and stationary regime, respectively, in the underlying LD-

QBD process. See, e.g., the papers by De Nitto Personè and Grassi [17], Gaver et al. [20], and Gómez-Corral et al. [22] for a detailed discussion on LD-QBD processes and their applications in the context of varicella-zoster virus infections.

In order to further clarify differences between the sensitive and the resistant bacterial strains, our objective here is to characterize the probability law of the *exact* reproduction number $\mathcal{R}_{exact,0}$ (Artalejo and López-Herrero [6]; Gómez-Corral et al. [24]) by decomposing this number into two random contributions according to the fact that infections generated by patients are due to the sensitive and the resistant bacteria. The work to be presented here is part of our ongoing study on the use of Markov chains, including LD-QBD processes, and related matrix-analytic methods in a variety of stochastic epidemic models, such as SIS and SIR models with two strains and cross-immunity (Almaraz and Gómez-Corral [2]; Amador et al. [4]), discrete and continuous versions of SIS models (Chalub and Sousa [11]; Gómez-Corral et al. [23]), quarantine of hosts (Amador and Gómez-Corral [5]), limited resources in epidemics (Amador and López-Herrero [3]) and vaccination strategies (Fernández and Gómez-Corral [18]; Gamboa and López-Herrero [19]), among others.

This article is organized as follows. Section 2 provides the mathematical description of a Markov chain model for the potential spread of a single bacterial species in a hospital ward where patients are accommodated in beds and may either be free of bacteria or carry antibiotic-sensitive or resistant bacteria. In particular, the model is first formulated as a LD-QBD process and then related to the deterministic model of Lipsitch et al. [27]. In Section 3 the propagation potential of the bacterial strains in early stages of the outbreak is studied in terms of suitably defined versions $\mathcal{R}^S_{exact,0}$ and $\mathcal{R}^R_{exact,0}$ of the *exact* reproductive number for the sensitive and the antibiotic-resistant bacterial strains, when the focus is on infections generated from a predetermined bed and an invasion time. In Sections 4 and 5, a discussion of numerical experiments and concluding remarks are presented.

2 Mathematical model description: a Markov chain model

In this work, we are concerned with a stochastic SIS model with two strains of a single bacterial species and partial cross-immunity for the bacterial transmission dynamics in a hospital ward where patients –who are accommodated in N beds– may carry bacterial strains that are either sensitive or resistant to a first antimicrobial agent, referred as drug 1, or they may be free of bacteria. The infection of a patient by one bacterial strain is assumed to provide immunity against the other strain, whence there is no coinfection. Resistance to a second antimicrobial agent, referred as drug 2, is not present in the bacteria. Both antimicrobial agents are assumed to be administrated in a prophylactic manner, which means that patients routinely receive drugs 1 and 2 at a rate which does not depend on whether or not they are colonized with bacteria; more concretely, treatment with drug 1 clears carriage of sensitive bacteria at rate τ_1 per day, and treatment with drug 2 clears carriage of both bacterial strains at rate τ_2 per day. Mutation from the sensitive to the

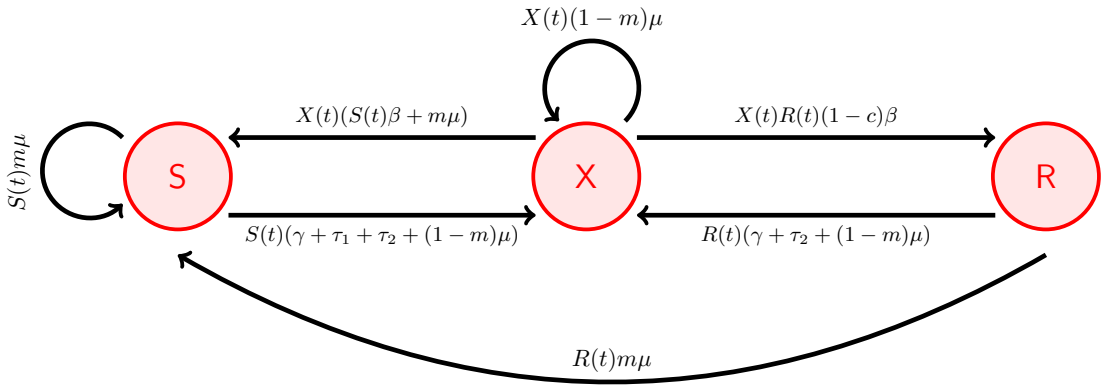

Figure 1: Diagram of transitions among compartments

resistant bacterial strain is not possible during the timescales of the outbreak, nor vice versa.

Bacteria may be transmitted between patients via direct contacts, which turns a patient who is free of bacteria into colonized with either sensitive bacteria at rate β per day, or resistant bacteria at rate $(1-c)\beta$ per day, where β is the per capita infection rate and $c \in (0,1)$ is the fitness cost of resistance to drug 1. Patients are assumed to be admitted by and discharged from the hospital ward[1] at rate μ per day, in such a way that they are replaced instantly by new patients who either are colonized with sensitive bacteria or are free of bacteria with proportion m and $1-m$, respectively, where m amounts to the proportion of people colonized with sensitive bacteria in the population at large. Spontaneous clearance of bacteria is seen to occur at rate γ per day.

Under the assumption of exponentially distributed sojourn times, the state of the hospital ward may be captured by means of a time-homogeneous continuous-time Markov chain $\mathcal{X} = \{(S(t)+R(t), R(t)) : t \geq 0\}$, where $S(t)$ and $R(t)$ record the number of patients colonized with sensitive and resistant bacteria, respectively, at time t. This results in the number $X(t) = N - S(t) - R(t)$ of patients who are free of bacteria. The bivariate process $\mathcal{X}$ can be seen as a LD-QBD process taking values in the finite set $\mathcal{S} = \cup_{i=0}^{N} l(i)$ with *levels* $l(i) = \{(i,j) : j \in \{0,...,i\}\}$, for integers $i \in \{0,...,N\}$. To be concrete, the infinitesimal dynamics of $\mathcal{X}$ are governed by the following non-vanishing transition rates from state (i,j)

[1]Hereinafter we will use the term *discharge from the hospital unit* to refer to the abandonment of the hospital ward due to any cause, such as the transfer of the patient to his home or another hospital ward, and his possible death.

to state (i', j'):

$$q_{(i,j),(i',j')} = \begin{cases} (N-i)((i-j)\beta + m\mu), & \text{if } (i',j') = (i+1, j), \\ (N-i)j(1-c)\beta, & \text{if } (i',j') = (i+1, j+1), \\ jm\mu, & \text{if } (i',j') = (i, j-1), \\ j(\gamma + \tau_2 + (1-m)\mu), & \text{if } (i',j') = (i-1, j-1), \\ (i-j)(\gamma + \tau_1 + \tau_2 + (1-m)\mu), & \text{if } (i',j') = (i-1, j), \end{cases}$$

for states $(i, j), (i', j') \in \mathcal{S}$ with $(i', j') \neq (i, j)$. Clearly, $q_{(i,j)(i,j+1)} = 0$. The transitions above represent, respectively, $X \to S$, $X \to R$, $R \to S$, $R \to X$, $S \to X$, and $S \to R$; see Figure 1 for further details. Furthermore $q_{(i,j),(i,j)} = -q_{(i,j)}$, where

$$q_{(i,j)} = (N-i)((i-jc)\beta + m\mu) + (i-j)(\gamma + \tau_1 + \tau_2 + (1-m)\mu) + j(\gamma + \tau_2 + \mu).$$

In the above description, two *hidden* events for process $\mathcal{X}$ can occur due to the replacement of a patient who is discharged from the hospital ward by a newly admitted patient who belongs to the same compartment; i.e., the process $\mathcal{X}$ does not allow us to record a transition from state (i, j) to (i, j), which occurs with rate $(N-i)(1-m)\mu + (i-j)m\mu$. This corresponds to a change in the time scale, without further effects in the final states and associated probability.

2.1 The Markov chain model *versus* its deterministic counterpart

The proposed Markov chain model is a stochastic realization of the deterministic model introduced in [27]. In that case, it is considered the set of ordinary differential equations

$$\begin{aligned} s' &= m\mu + \frac{\beta s x}{s+r+x} - (\gamma + \tau_1 + \tau_2 + \mu)s, \\ r' &= \frac{(1-c)\beta r x}{s+r+x} - (\gamma + \tau_2 + \mu)r, \\ x' &= (1-m)\mu + (\gamma + \tau_1 + \tau_2)s + (\gamma + \tau_2)r - \frac{\beta s x}{s+r+x} - \frac{(1-c)\beta r x}{s+r+x} - \mu x, \end{aligned}$$

where $s(t)$, $r(t)$, and $x(t)$ represent the proportion of patients colonized with sensitive and resistant bacteria, and the fraction of patients free of bacteria, respectively, at time t, and β is the transmission rate. We did not assume *a priori* the normalization, for reasons that will be clarified in the sequel. The normalization, however, follows from the simple fact that $(s+r+x)' = \mu(1-s-r-x)$, and, therefore, we may assume $s(t) + r(t) + x(t) = 1$, for all $t \geq 0$, and omit one of the equations.

Defining $z = s + r$ the above system is equivalent to

$$z' = m\mu + \beta(z - cr)(1-z) - (\gamma + \tau_1 + \tau_2 + \mu)z + \tau_1 r, \tag{1}$$

$$r' = r\Big((1-c)\beta(1-z) - (\gamma + \tau_2 + \mu)\Big). \tag{2}$$

It is possible to prove, in a very precise way, that the Markov chain introduced in the present manuscript converges in the large population limit to the model (1)–(2). More precisely, we show that the large population limit of the Markov chain is a first-order partial differential equation, see equation below, such that its characteristics are the trajectories of the solutions of the system (1)–(2). The proof follows ideas from [9]; see also [10, 11].

Namely, for the Markov chain, we consider the *master equation*

$$p\left(\frac{i'}{N},\frac{j'}{N},t+\Delta t\right)=p\left(\frac{i'}{N},\frac{j'}{N},t\right)+\sum_{(i,j)\neq(i',j')}q_{(i,j)(i',j')}p\left(\frac{i}{N},\frac{j}{N},t\right)\Delta t,$$

where $p(z,r,t)$ is the probability to find the Markov chain at state $(\lfloor Nz\rfloor,\lfloor Nr\rfloor)$ at time t. In the weak formulation, the last equation reads

$$\sum_{(i',j')}p\left(\frac{i'}{N},\frac{j'}{N},t+\Delta t\right)\varphi\left(\frac{i'}{N},\frac{j'}{N}\right)=\sum_{(i,j)}p\left(\frac{i}{N},\frac{j}{N},t\right)\sum_{(i',j')\neq(i,j)}q_{(i,j),(i'j')}\varphi\left(\frac{i'}{N},\frac{j'}{N}\right),$$

where φ is an adequate test function, i.e., $\varphi(z+\Delta z,r\pm\Delta r)=\varphi(z,r)+\Delta z\partial_z\varphi(z,r)+\Delta r\partial_r\varphi(z,r)+o(\Delta z,\Delta r)$. Therefore, it is seen that

$$\begin{aligned}
&\sum_{(i',j')}q_{(i,j)(i',j')}\varphi\left(\frac{i'}{N},\frac{j'}{N}\right)\\
&\quad=\varphi\left(\frac{i}{N},\frac{j}{N}\right)+\Big((N-i)\Big((i-j)\frac{\beta}{N}+m\mu+j(1-c)\beta\Big)-j(\gamma+\tau_2+\gamma+(1-m)\mu)\\
&\qquad-(i-j)(\gamma+\tau_1+\tau_2+(1-m)\mu)\Big)\frac{\Delta t}{N}\partial_z\varphi\left(\frac{i}{N},\frac{j}{N}\right)\\
&\qquad+\Big((N-i)\frac{\beta}{N}(1-c)-\mu m-(\tau_2+\gamma+\mu(1-m))\Big)\frac{j\Delta t}{N}\partial_r\varphi\left(\frac{i}{N},\frac{j}{N}\right)+o\left(\frac{\Delta t}{N}\right)\\
&\quad=\varphi\left(z,r\right)+\Delta t\Big(\Big((1-z)\beta(z-cr)+\mu m-z(\gamma+\tau_1+\tau_2+\mu)+r\tau_1\Big)\partial_z\varphi(z,r)\\
&\qquad+\Big((1-z)\beta(1-c)-\tau_2+\gamma+\mu)\Big)r\partial_r\varphi(z,r)+o\left(\frac{1}{N}\right)\Big).
\end{aligned}$$

After taking the limit $\Delta t\to 0$ and $N\to\infty$, we conclude that probabilities $p(z,r,t)$ satisfy the equation

$$\begin{aligned}
\partial_t p=&-\partial_z\Big((1-z)\beta(z-cr)+\mu m-z(\gamma+\tau_1+\tau_2+\mu+r\tau_1\Big)\\
&-\partial_r\Big(r\Big((1-z)\beta(1-c)-(\tau_2+\gamma+\mu)\Big)\Big).
\end{aligned}$$

The characteristics of this equation are the solutions of the system (z,r) defined above. Note the relevance of not assuming *a prior* the normalization, as the $1/N$ normalization in the transmission rate is explicitly used in order to have a well-defined limit.

Remark 1. *There is no specific reason to stop the Taylor expansion of the Markov chain model at the first order in* $1/N$*; in fact, the second order term will model random effects. The idea is clear in population genetic models (c.f. [9, 12]); in epidemiological models, the interpretation of the diffusion coefficient is not clear [11]. The resulting equation is a partial differential equation with degenerated coefficient and its rigorous mathematical analysis presents serious challenges [13, 16].*

3 The exact reproduction number $\mathcal{R}_{exact,0}$

Let us consider an invasion time, i.e., $S(0)+R(0) = 1$, and assume that the initially infected patient is accommodated in a *marked* bed. It is likely that the initially infected patient may be discharged from the hospital ward before recovering, in which case the newly admitted patient who settles into the marked bed instead may either be free of bacteria or colonized with sensitive bacteria. In the latter case, this means that the bacteria remains present in the hospital ward, with the marked bed being a source of bacterial transmission. Thus, the dynamics of bacterial dissemination during an early stage of the epidemic is not linked only to the initially infected individual, but to those patients who settle one after another in the marked bed.

We define here the exact reproduction number $\mathcal{R}_{exact,0}$ as the number of infections generated by the patients who are accommodated —one after another— in the marked bed before one of them is free of bacteria. The most remarkable feature of process $\mathcal{X}$ is the transmission of sensitive and resistant bacteria, whence we express the exact reproduction number $\mathcal{R}_{exact,0}$ in terms of two random contributions $\mathcal{R}^S_{exact,0}$ and $\mathcal{R}^R_{exact,0}$ according to the fact that infections are due to the sensitive bacterial strain and the resistant bacterial strain, respectively.

Remark 2. *In Ref. [27], the basic reproduction number*[2]

$$R_0 = \frac{\beta}{\gamma + \tau_2 + \mu}$$

is linked to a single patient colonized with resistant bacteria, who is hospitalized in a hypothetical hospital ward where all other inpatients entered uncolonized; i.e., secondary cases contributing to R_0 *are resistant infections generated by this initially colonized patient before either becoming free of bacteria or leaving the hospital ward. An interesting question, which will be addressed in Section 4, concerns the relationship between the expected number* $E[\mathcal{R}^R_{exact,0}|(S(0)+R(0), R(0)) = (1,1)]$ *and its deterministic counterpart* R_0*.*

In this section, our objective is to determine the joint probability law of $(\mathcal{R}^S_{exact,0}, \mathcal{R}^R_{exact,0})$ by evaluating the conditional probabilities

$$P\left((\mathcal{R}^S_{exact,0}, \mathcal{R}^R_{exact,0}) = (s,0)\middle|\, (S(0)+R(0), R(0)) = (1,0)\right),$$
$$P\left((\mathcal{R}^S_{exact,0}, \mathcal{R}^R_{exact,0}) = (s,r)\middle|\, (S(0)+R(0), R(0)) = (1,1)\right),$$

[2]In the terminology of [27], the parameter β is the transmission rate, which is equivalent to $N\beta$ if β denotes the per capita infection rate.

for integers $s, r \in \mathbb{N}_0$. In evaluating these probabilities, we first denote the *status* of the patient who is accommodated in the marked bed at time t by $B(t)$ —in such a way that $B(t) = 0$ if the patient is free of bacteria, and $B(t) = 1_S$ and 1_R if the patient is colonized with sensitive and resistant bacteria, respectively—, and we define the following more general conditional probabilities:

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

$$P_{(i,j),1_S}(s, r) = P\left((\mathcal{R}^S_{exact,0}, \mathcal{R}^R_{exact,0}) = (s, r) \middle| (S(0) + R(0), R(0)) = (i, j), B(0) = 1_S\right),$$

for $s, r \in \mathbb{N}_0$. Clearly, $P_{(i,j),1_S}(s, r) = 0$ if $r \in \mathbb{N}$, for $i \in \{1, ..., N\}$ and $j \in \{0, ..., i-1\}$.

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

$$P_{(i,j),1_R}(s, r) = P\left((\mathcal{R}^S_{exact,0}, \mathcal{R}^R_{exact,0}) = (s, r) \middle| (S(0) + R(0), R(0)) = (i, j), B(0) = 1_R\right),$$

for $s, r \in \mathbb{N}_0$.

3.1 The special case $B(0) = 1_S$

In this subsection, we derive an iterative procedure that, starting from the family of conditional probabilities $\{P_{(i,j),1_S}(0, 0) : i \in \{1, ..., N\}, j \in \{0, ..., i-1\}\}$, evaluates the family of probabilities $\{P_{(i,j),1_S}(s, 0) : i \in \{1, ..., N\}, j \in \{0, ..., i-1\}\}$ in terms of the probabilities in $\{P_{(i,j),1_S}(s-1, 0) : i \in \{1, ..., N\}, j \in \{0, ..., i-1\}\}$, for $s \in \mathbb{N}$.

We use first-step analysis to obtain the system of linear equations

$$\begin{aligned}
P_{(i,0),1_S}(0, 0) = {} & \frac{\gamma + \tau_1 + \tau_2 + (1-m)\mu}{q_{(i,0)}} + \frac{(i-1)(\gamma + \tau_1 + \tau_2 + (1-m)\mu)}{q_{(i,0)}} P_{(i-1,0),1_S}(0, 0) \\
& + \left(\frac{(i-1)m\mu}{q_{(i,0)}} + \frac{(N-i)(1-m)\mu}{q_{(i,0)}}\right) P_{(i,0),1_S}(0, 0) \\
& + \frac{(N-i)((i-1)\beta + m\mu)}{q_{(i,0)}} P_{(i+1,0),1_S}(0, 0), \qquad (3) \\
P_{(i,0),1_S}(s, 0) = {} & \frac{m\mu}{q_{(i,0)}} P_{(i,0),1_S}(s-1, 0) + \frac{(N-i)\beta}{q_{(i,0)}} P_{(i+1,0),1_S}(s-1, 0) \\
& + \frac{(i-1)(\gamma + \tau_1 + \tau_2 + (1-m)\mu)}{q_{(i,0)}} P_{(i-1,0),1_S}(s, 0) \\
& + \left(\frac{(i-1)m\mu}{q_{(i,0)}} + \frac{(N-i)(1-m)\mu}{q_{(i,0)}}\right) P_{(i,0),1_S}(s, 0) \\
& + \frac{(N-i)((i-1)\beta + m\mu)}{q_{(i,0)}} P_{(i+1,0),1_S}(s, 0), \qquad (4)
\end{aligned}$$

for integers $i \in \{1, ..., N\}$ and $s \in \mathbb{N}$. Equations (3) and (4) can be readily written as a single equation in matrix form by using column vectors $\mathbf{P}_{0,1_S}(s)$, for $s \in \mathbb{N}_0$, and $\mathbf{p}_{0,1_S}$ with

i-th entries $P_{(i,0),1_S}(s,0)$ and $q^{-1}_{(i,0)}(\gamma+\tau_1+\tau_2+(1-m)\mu)$, respectively, for $i \in \{1,...,N\}$. Specifically, it is seen that

$$\mathbf{P}_{0,1_S}(s) = (\mathbf{I}_N - \mathbf{C}_0(0))^{-1}\Big(\delta_{s,0}\mathbf{p}_{0,1_S} + (1-\delta_{s,0})\mathbf{B}_0\mathbf{P}_{0,1_S}(s-1)\Big), \tag{5}$$

where $\mathbf{I}_a$ denotes the identity matrix of order a, $\delta_{a,b}$ represents the Kronecker delta, and $\mathbf{B}_0$ and $\mathbf{C}_0(0)$ are suitably defined matrices of coefficients; see Appendix A.

For initial states $(i,j) \in \mathcal{S}$ with $i \in \{j+1,...,N\}$ and $j \in \{1,...,N-1\}$, a similar approach leads us to the following equalities for the column vectors $\mathbf{P}_{j,1_S}(s)$, for $j \in \{1,...,N-1\}$ and $s \in \mathbb{N}_0$, with i-th entry $P_{(j+i,j),1_S}(s,0)$, for $i \in \{1,...,N-j\}$:

$$\begin{aligned}\mathbf{P}_{j,1_S}(s) &= \delta_{s,0}\mathbf{p}_{j,1_S} + (1-\delta_{s,0})\mathbf{B}_j\mathbf{P}_{j,1_S}(s-1)\\ &\quad + \mathbf{C}_{j-1}(1)\mathbf{P}_{j-1,1_S}(s) + (1-\delta_{j,N-1})\left(\mathbf{C}_j(0)\mathbf{P}_{j,1_S}(s) + \mathbf{C}_{j+1}(2)\mathbf{P}_{j+1,1_S}(s)\right),\end{aligned} \tag{6}$$

where the column vector $\mathbf{p}_{j,1_S}$ has i-entry $q^{-1}_{(j+i,j)}(\gamma+\tau_1+\tau_2+(1-m)\mu)$, for $i \in \{1,...,N-j\}$, and $\mathbf{B}_j$, $\mathbf{C}_j(0)$, $\mathbf{C}_{j-1}(1)$ and $\mathbf{C}_{j+1}(2)$ are matrices of coefficients; see Appendix B.

For a fixed value $s \in \mathbb{N}_0$, Eq. (6) can be seen as a tridiagonal-by-blocks system of linear equations for the unknown vectors $\mathbf{P}_{j,1_S}(s)$, for $j \in \{1,...,N-1\}$, which can be solved using block-Gaussian elimination in terms of previously evaluated vectors $\mathbf{P}_{j,1_S}(s-1)$.

Theorem 1. *For $s \in \mathbb{N}_0$, the column vectors in $\{\mathbf{P}_{j,1_S}(s) : j \in \{1,...,N-1\}\}$ satisfy the recurrence equations*

$$\mathbf{P}_{j,1_S}(s) = \mathbf{h}_{j,1_S}(s) + (1-\delta_{j,N-1})\mathbf{H}^{-1}_{j,1_S}\mathbf{C}_{j+1}(2)\mathbf{P}_{j+1,1_S}(s), \tag{7}$$

with

$$\begin{aligned}\mathbf{h}_{j,1_S}(s) &= \mathbf{H}^{-1}_{j,1_S}\Big(\delta_{s,0}\mathbf{p}_{j,1_S} + (1-\delta_{s,0})\mathbf{B}_j\mathbf{P}_{j,1_S}(s-1)\\ &\qquad + \mathbf{C}_{j-1}(1)\Big(\delta_{j,1}\mathbf{P}_{0,1_S}(s) + (1-\delta_{j,1})\mathbf{h}_{j-1,1_S}(s)\Big)\Big),\\ \mathbf{H}_{j,1_S} &= \mathbf{I}_{N-j} - (1-\delta_{j,N-1})\mathbf{C}_j(0) - (1-\delta_{j,1})\mathbf{C}_{j-1}(1)\mathbf{H}^{-1}_{j-1,1_S}\mathbf{C}_j(2),\end{aligned}$$

where $\mathbf{P}_{0,1_S}(s)$ is given by (5).

A point worth mentioning is that the structured form of (6) also allows us to derive an iterative scheme for computing the moments of the random number $\mathcal{R}^S_{exact,0}$ on the sample paths of process $\mathcal{X}$ satisfying $\{\mathcal{R}^R_{exact,0} = 0\}$. More particularly, in terms of the generating functions

$$\varphi_{j,1_S}(x) = \sum_{s=0}^{\infty} x^s \mathbf{P}_{j,1_S}(s), \quad |x| \le 1,$$

for integers $j \in \{0,...,N-1\}$, Eqs. (5)-(6) are solved to yield the expressions

$$\begin{aligned}\varphi_{0,1_S}(x) &= (\mathbf{I}_N - \mathbf{C}_0(0) - x\mathbf{B}_0)^{-1}\,\mathbf{p}_{0,1_S},\\ \varphi_{j,1_S}(x) &= \mathbf{g}_{j,1_S}(x) + (1-\delta_{j,N-1})\mathbf{G}^{-1}_{j,1_S}(x)\mathbf{C}_{j+1}(2)\varphi_{j+1,1_S}(x),\end{aligned}$$

for $j \in \{1, ..., N-1\}$ and $|x| \leq 1$, where

$$\mathbf{g}_{j,1_S}(x) = \mathbf{G}^{-1}_{j,1_S}(x)\Big(\mathbf{p}_{j,1_S} + \mathbf{C}_{j-1}(1)\Big(\delta_{j,1}\varphi_{0,1_S}(x) + (1-\delta_{j,1})\mathbf{g}_{j-1,1_S}(x)\Big)\Big),$$
$$\mathbf{G}_{j,1_S}(x) = \mathbf{I}_{N-j} - x\mathbf{B}_j - (1-\delta_{j,N-1})\mathbf{C}_j(0) - (1-\delta_{j,1})\mathbf{C}_{j-1}(1)\mathbf{G}^{-1}_{j-1,1_S}(x)\mathbf{C}_j(2).$$

In terms of the column vectors

$$\varphi^{(n)}_{j,1_S} = \left.\frac{d^n\varphi_{j,1_S}(x)}{dx^n}\right|_{x=1},$$

for $j \in \{0, ..., N-1\}$, the computation of factorial moments of $\mathcal{R}^S_{exact,0}$ on the sample paths of process $\mathcal{X}$ satisfying $\{\mathcal{R}^R_{exact,0} = 0\}$ is possible, as shown in the result below.

Corollary 1. *For $n \in \mathbb{N}$, the column vectors $\{\varphi^{(n)}_{j,1_S} : j \in \{0, ..., N-1\}\}$ can be iteratively computed, starting with $\varphi^{(0)}_{j,1_S} = \mathbf{1}_N$, from the equalities*

$$\varphi^{(n)}_{0,1_S} = n\left(\mathbf{I}_N - \mathbf{C}_0(0) - \mathbf{B}_0\right)^{-1}\mathbf{B}_0\varphi^{(n-1)}_{0,1_S},$$
$$\varphi^{(n)}_{j,1_S} = \mathbf{g}^{(n)}_{j,1_S} + (1-\delta_{j,N-1})\mathbf{G}^{-1}_{j,1_S}(1)\mathbf{C}_{j+1}(2)\varphi^{(n)}_{j+1,1_S},$$

for $j \in \{1, ..., N-1\}$, where

$$\mathbf{g}^{(n)}_{j,1_S} = \mathbf{G}^{-1}_{j,1_S}(1)\left(n\mathbf{B}_j\varphi^{(n-1)}_{j,1_S} + \mathbf{C}_{j-1}(1)\left(\delta_{j,1}\varphi^{(n)}_{0,1_S} + (1-\delta_{j,1})\mathbf{g}^{(n)}_{j-1,1_S}\right)\right),$$

and $\mathbf{1}_a$ is a column vector of order a of 1's.

In particular, the first entry of the column vector

$$\left(\mathbf{I}_N - \mathbf{C}_0(0) - \mathbf{B}_0\right)^{-1}\mathbf{B}_0\mathbf{1}_N$$

is found to be the mean value of $\mathcal{R}^S_{exact,0}$ at an invasion time when the initially infected patient is colonized with sensitive bacteria; i.e., it corresponds to $E[\mathcal{R}^S_{exact,0}|(S(0)+R(0), R(0)) = (1,0)]$. This is derived by noting that, since $P_{(1,0),1_S}(s,r) = 0$ if $r \in \mathbb{N}$, this mean value amounts to the expectation $E[\mathcal{R}^S_{exact,0}1\{\mathcal{R}^R_{exact,0} = 0\}|(S(0)+R(0), R(0)) = (1,0), B(0) = 1_S]$, and $\varphi^{(0)}_{0,1_S} = \varphi_{0,1_S}(1)$.

3.2 The special case $B(0) = 1_R$

In order to evaluate the conditional probabilities $\{P_{(i,j),1_R}(s,r) : i \in \{1, ..., N\},\ j \in \{1, ..., i\}\}$, for integers $s, r \in \mathbb{N}_0$, and related moments of $(\mathcal{R}^S_{exact,0}, \mathcal{R}^R_{exact,0})$ we first introduce the column vectors $\mathbf{P}_{j,1_R}(s,r)$ and $\mathbf{p}_{j,1_R}$, for $j \in \{1, ..., N\}$, with i-th entries $P_{(j-1+i,j),1_R}(s,r)$ and $q^{-1}_{(j-1+i,j)}(\gamma + \tau_2 + (1-m)\mu)$, respectively, if $i \in \{1, ..., N-j+1\}$. We

also consider

$$\varphi^{(n)}_{j,1_R} = \left.\frac{d^n \varphi_{j,1_R}(x)}{dx^n}\right|_{x=1},$$
$$\phi^{(n,\cdot)}_{j,1_R} = \left.\frac{\partial^n \phi_{j,1_R}(x,1)}{\partial x^n}\right|_{x=1},$$
$$\phi^{(\cdot,m)}_{j,1_R} = \left.\frac{\partial^m \phi_{j,1_R}(1,y)}{\partial y^m}\right|_{y=1},$$

for $j \in \{1,...,N\}$ and $n,m \in \mathbb{N}_0$, where $\varphi_{j,1_R}(x) = \sum_{s=0}^{\infty} x^s \mathbf{P}_{j,1_R}(s,0)$ and $\phi_{j,1_R}(x,y) = \sum_{s=0}^{\infty}\sum_{r=1}^{\infty} x^s y^r \mathbf{P}_{j,1_R}(s,r)$, for $|x|,|y| \leq 1$. We then use first-step analysis to yield the theorems below. The proofs mostly follow the argument yielding Theorem 1 and thus are omitted.

Theorem 2. *For $s \in \mathbb{N}_0$, the column vectors $\{\mathbf{P}_{j,1_R}(s,0) : j \in \{1,...,N\}\}$ can be written in the form*

$$\mathbf{P}_{1,1_R}(s,0) = (\mathbf{I}_N - \mathbf{D}_1(0))^{-1}\Big(\delta_{s,0}\mathbf{p}_{1,1_R} + (1-\delta_{s,0})\mathbf{E}_1\mathbf{P}_{0,1_S}(s-1)\Big),$$
$$\mathbf{P}_{j,1_R}(s,0) = \mathbf{h}_{j,1_R}(s,0) + (1-\delta_{j,N})\mathbf{H}^{-1}_{j,1_R}\mathbf{D}_{j+1}(2)\mathbf{P}_{j+1,1_R}(s,0),$$

for $j \in \{2,...,N\}$, where $\mathbf{P}_{0,1_S}(s-1)$ is evaluated from (5),

$$\mathbf{h}_{j,1_R}(s,0) = \mathbf{H}^{-1}_{j,1_R}\Big(\delta_{s,0}\mathbf{p}_{j,1_R} + (1-\delta_{s,0})\mathbf{E}_j\mathbf{P}_{j-1,1_S}(s-1)$$
$$+ \mathbf{D}_{j-1}(1)\Big(\delta_{j,2}\mathbf{P}_{1,1_R}(s,0) + (1-\delta_{j,2})\mathbf{h}_{j-1,1_R}(s,0)\Big)\Big),$$
$$\mathbf{H}_{j,1_R} = \mathbf{I}_{N-j+1} - (1-\delta_{j,N})\mathbf{D}_j(0) - (1-\delta_{j,2})\mathbf{D}_{j-1}(1)\mathbf{H}^{-1}_{j-1,1_R}\mathbf{D}_j(2),$$

and $\mathbf{D}_j(0)$, $\mathbf{D}_{j-1}(1)$, $\mathbf{D}_{j+1}(2)$ and $\mathbf{E}_j$ are suitably defined matrices of coefficients; see Appendix C.

Theorem 3. *For $s \in \mathbb{N}_0$ and $r \in \mathbb{N}$, the column vectors in $\{\mathbf{P}_{j,1_R}(s,r) : j \in \{1,...,N\}\}$ have the form*

$$\mathbf{P}_{1,1_R}(s,r) = (\mathbf{I}_N - \mathbf{D}_1(0))^{-1}\mathbf{F}_1\mathbf{P}_{2,1_R}(s,r-1),$$
$$\mathbf{P}_{j,1_R}(s,r) = \mathbf{h}_{j,1_R}(s,r) + (1-\delta_{j,N})\mathbf{H}^{-1}_{j,1_R}\mathbf{D}_{j+1}(2)\mathbf{P}_{j+1,1_R}(s,r),$$

for $j \in \{2,...,N\}$, where

$$\mathbf{h}_{j,1_R}(s,r) = \mathbf{H}^{-1}_{j,1_R}\Big((1-\delta_{j,N})\mathbf{F}_j\mathbf{P}_{j+1,1_R}(s,r-1)$$
$$+ \mathbf{D}_{j-1}(1)\Big(\delta_{j,2}(1-\delta_{j,N})\mathbf{P}_{1,1_R}(s,r) + (1-\delta_{j,2})\mathbf{h}_{j-1,1_R}(s,r)\Big)\Big),$$

and matrices $\mathbf{F}_j$ are specified in Appendix C.

The factorial conditional moments of $\mathcal{R}^S_{exact,0}$ on the sets $\{\mathcal{R}^R_{exact,0}=0\}$ and $\{\mathcal{R}^R_{exact,0}>0\}$, provided that $(S(0)+R(0),R(0))=(i,j)$ and $B(0)=1_R$, for integers $i\in\{j,...,N\}$ and $j\in\{1,...,N\}$, are given by the entries of $\varphi^{(n)}_{j,1_R}$ and $\phi^{(n,\cdot)}_{j,1_R}$, respectively. As a result, the mean value $E[\mathcal{R}^S_{exact,0}|(S(0)+R(0),R(0))=(1,1)]$ is given by the first entry of $\varphi^{(1)}_{1,1_R}+\phi^{(1,\cdot)}_{1,1_R}$.

Corollary 2. *For $n\in\mathbb{N}$, it is seen that*

(i) The column vectors $\{\varphi^{(n)}_{j,1_R}:j\in\{1,...,N\}\}$ are found to satisfy

$$\varphi^{(n)}_{1,1_R}=(\mathbf{I}_N-\mathbf{D}_1(0))^{-1}\,\mathbf{E}_1\Big(\varphi^{(n)}_{0,1_S}+n\varphi^{(n-1)}_{0,1_S}\Big),$$
$$\varphi^{(n)}_{j,1_R}=\mathbf{g}^{(n)}_{j,1_R}+(1-\delta_{j,N})\mathbf{H}^{-1}_{j,1_R}\mathbf{D}_{j+1}(2)\varphi^{(n)}_{j+1,1_R},$$

for $j\in\{2,...,N\}$, where vectors $\varphi^{(n)}_{0,1_S}$, for $n\in\mathbb{N}_0$, are evaluated from Corollary 1 and

$$\mathbf{g}^{(n)}_{j,1_R}=\mathbf{H}^{-1}_{j,1_R}\Big(\mathbf{E}_j\Big(n\varphi^{(n-1)}_{j-1,1_S}+\varphi^{(n)}_{j-1,1_S}\Big)+\mathbf{D}_{j-1}(1)\Big(\delta_{j,2}\varphi^{(n)}_{1,1_R}+(1-\delta_{j,2})\mathbf{g}^{(n)}_{j-1,1_R}\Big)\Big).$$

(ii) The column vectors $\{\phi^{(n,\cdot)}_{j,1_R}:j\in\{1,...,N\}\}$ have the form

$$\phi^{(n,\cdot)}_{j,1_R}=\mathbf{l}^{(n,\cdot)}_{j,1_R}+(1-\delta_{j,N})\mathbf{L}^{-1}_{j,1_R}\Big(\mathbf{F}_j+(1-\delta_{j,1})\mathbf{D}_{j+1}(2)\Big)\phi^{(n,\cdot)}_{j+1,1_R},$$

where

$$\mathbf{l}^{(n,\cdot)}_{j,1_R}=\mathbf{L}^{-1}_{j,1_R}\left((1-\delta_{j,1})\mathbf{D}_{j-1}(1)\mathbf{l}^{(n,\cdot)}_{j-1,1_R}+(1-\delta_{j,N})\mathbf{F}_j\varphi^{(n)}_{j+1,1_R}\right),$$

and matrices $\mathbf{L}_{j,1_R}$, for $j\in\{1,...,N\}$, are defined by

$$\mathbf{L}_{j,1_R}=\mathbf{I}_{N-j+1}-(1-\delta_{j,N})\mathbf{D}_j(0)-(1-\delta_{j,1})\mathbf{L}^{-1}_{j-1,1_R}\mathbf{D}_{j-1}(1)\Big(\mathbf{F}_{j-1}+(1-\delta_{j,2})\mathbf{D}_j(2)\Big).$$

Finally, the mean value $E[\mathcal{R}^R_{exact,0}|(S(0)+R(0),R(0))=(1,1)]$ can be derived as the first entry of $\phi^{(\cdot,1)}_{1,1_R}$ and, in a more general way, column vectors $\phi^{(\cdot,m)}_{j,1_R}$, for $j\in\{1,...,N\}$, record the m-th factorial conditional moments of $\mathcal{R}^R_{exact,0}$, provided that $(S(0)+R(0),R(0))=(i,j)$ and $B(0)=1_R$, for $i\in\{j,...,N\}$.

Corollary 3. *For $m\in\mathbb{N}$, the column vectors $\{\phi^{(\cdot,m)}_{j,1_R}:j\in\{1,...,N\}\}$ are specified by*

$$\phi^{(\cdot,m)}_{j,1_R}=\mathbf{l}^{(\cdot,m)}_{j,1_R}+(1-\delta_{j,N})\mathbf{L}^{-1}_{j,1_R}\Big(\mathbf{F}_j+(1-\delta_{j,1})\mathbf{D}_{j+1}(2)\Big)\phi^{(\cdot,m)}_{j+1,1_R},$$

where

$$\mathbf{l}^{(\cdot,m)}_{j,1_R}=\mathbf{L}^{-1}_{j,1_R}\left((1-\delta_{j,1})\mathbf{D}_{j-1}(1)\mathbf{l}^{(\cdot,m)}_{j-1,1_R}+(1-\delta_{j,N})\mathbf{F}_j\left(\delta_{m,1}\varphi_{j+1,1_R}(1)+m\phi^{(\cdot,m-1)}_{j+1,1_R}\right)\right).$$

4 Numerical experiments and discussion

In this section, we present some numerical experiments to illustrate the variability of the probability law of the random contributions $\mathcal{R}^R_{exact,0}$ and $\mathcal{R}^S_{exact,0}$ to the exact reproduction number $\mathcal{R}_{exact,0}$, mainly as a function of the proportion m of individuals who enter the hospital carrying sensitive bacteria. We consider a hospital ward that consists of one marked bed, where a patient colonized with resistant bacteria is accommodated at time $t = 0$, and nineteen beds accommodating initially uncolonized patients; i.e., $R(0) = 1$, $S(0) = 0$ and $X(0) = 19$. It is assumed that inpatients contact each other, on average, in 1 *day*, whence the per capita infection rate is given by $\beta = N^{-1}$ with $N = 20$.

In our numerical experiments, the fitness difference between sensitive and resistant bacterial strains is relatively small ($c = 0.05$), and scenarios in Figures 2-5 are specified from suitable choices of the average duration of hospital stay $\mu^{-1} \in \{7, 14, 21\}$ *days*, the average time from admission or colonization until spontaneous clearance of bacterial carriage $\gamma^{-1} \in \{30, 45, 60\}$ *days*, and the proportion $m \in [0.2, 1.0]$ of admitted already colonized with sensitive bacteria. Drugs 1 and 2 are assumed to be effective on colonized patients, on average, in $\tau_1^{-1} \in \{2.5, 5, 10\}$ *days* and $\tau_2^{-1} \in \{5, 10, 20\}$ *days*, respectively. For details on these values of parameters and published sources for them, we refer the reader to Ref. [27] and references therein.

Figure 2 (respectively, Figure 3) illustrates the dynamics of colonization with resistant and sensitive bacteria in terms of the basic reproduction number R_0, and of the expectations of the random numbers $\mathcal{R}^R_{exact,0}$ and $\mathcal{R}^S_{exact,0}$, which are plotted as a function of the proportion m, for values of $\mu^{-1} \in \{7, 14, 21\}$ *days*, $\gamma^{-1} \in \{30, 45, 60\}$ *days*, $\tau_1^{-1} = 5$ *days* and $\tau_2^{-1} = 10$ *days* (respectively, $\tau_1^{-1} \in \{2.5, 5, 10\}$ *days*, $\tau_2^{-1} \in \{5, 10, 20\}$ *days*, $\mu^{-1} = 14$ *days* and $\gamma^{-1} = 30$ *days*). A first important observation is that, in our experiments, values of R_0 are found to be greater than the corresponding values for the expectation of $\mathcal{R}^R_{exact,0}$, regardless of the parameters. This observation is counterintuitive because the random length of the interval during which secondary cases contribute to $\mathcal{R}^R_{exact,0}$ is likely to be longer than the length of that involved in R_0. However, it can be understood as a consequence of the fact that R_0 is formally intended to be an index of the potential, but not exact, contagiousness of the resistant bacteria at early stages of the epidemic and, therefore, its values in Ref. [27] are only affected by the dynamics of the inpatient-to-inpatient contact process until either the treatment with drug 2 or other non-therapeutic reasons clear carriage of resistant bacteria on the initially colonized patient, or this patient's hospital stay ends.

It is seen that, as intuition tells us, the more individuals already colonized with sensitive bacteria are admitted to the hospital, the less propagation of resistant bacteria will be observed as well as the greater propagation of sensitive bacteria from the marked bed. This means that, in reducing carriage of resistant bacteria at an early stage of the epidemic, any intervention based on admitting more individuals already colonized with sensitive bacteria will prevent the transmission of the resistant strain within the hospital ward, but will increase the transmission of the sensitive one. In a similar way, an intervention based on reducing the hospital stay will reduce the carriage of resistant bacteria, while the prevalence

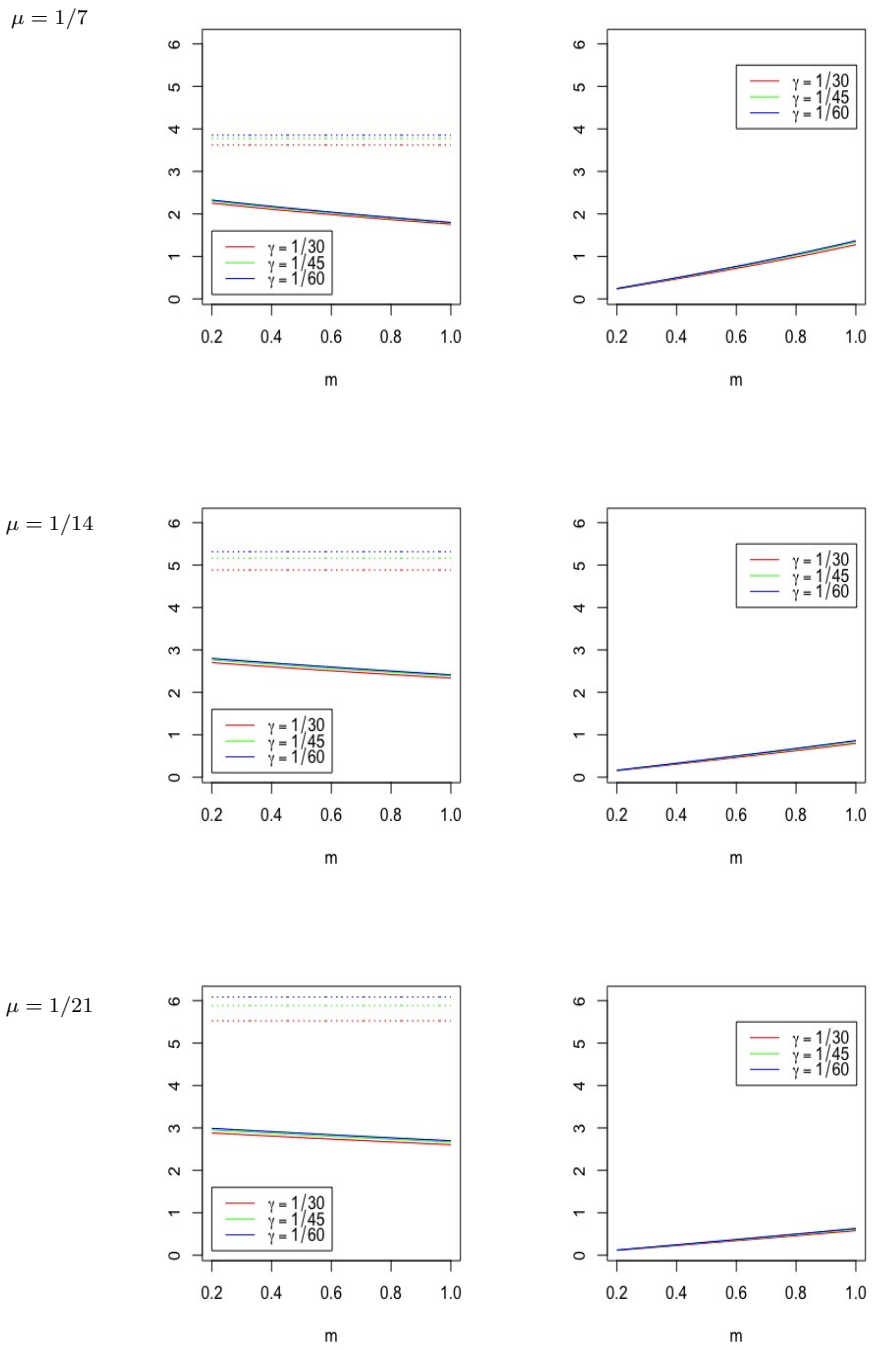

Figure 2: The basic reproduction number R_0 (left column, dotted lines), and expected values $E[\mathcal{R}^R_{exact,0}|(S(0)+R(0),R(0))=(1,1)$ (left column, solid lines) and $E[\mathcal{R}^S_{exact,0}|(S(0)+R(0),R(0))=(1,1)$ (right column) as a function of m, for values of $\mu^{-1}\in\{7,14,21\}$ *days*, $\gamma^{-1}\in\{30,45,60\}$ *days*, $\tau_1^{-1}=5$ *days* and $\tau_2^{-1}=10$ *days*.

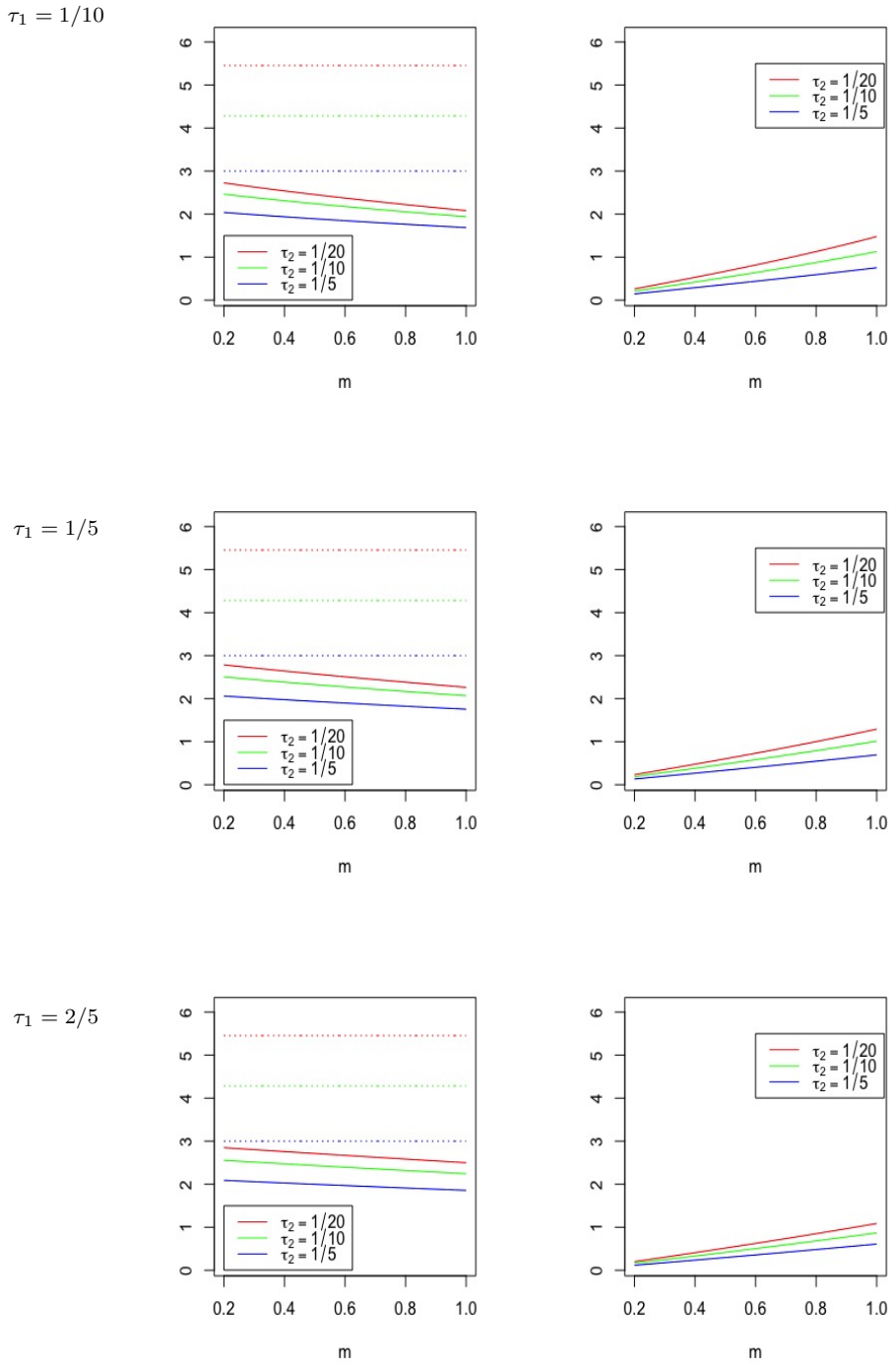

Figure 3: The basic reproduction number R_0 (left column, dotted lines), and expected values $E[\mathcal{R}^R_{exact,0}|(S(0)+R(0),R(0))=(1,1)$ (left column, solid lines) and $E[\mathcal{R}^S_{exact,0}|(S(0)+R(0),R(0))=(1,1)$ (right column) as a function of m, for values of $\tau_1^{-1} \in \{2.5,5,10\}$ *days*, $\tau_2^{-1} \in \{5,10,20\}$ *days*, $\mu^{-1}=14$ *days* and $\gamma^{-1}=30$ *days*.

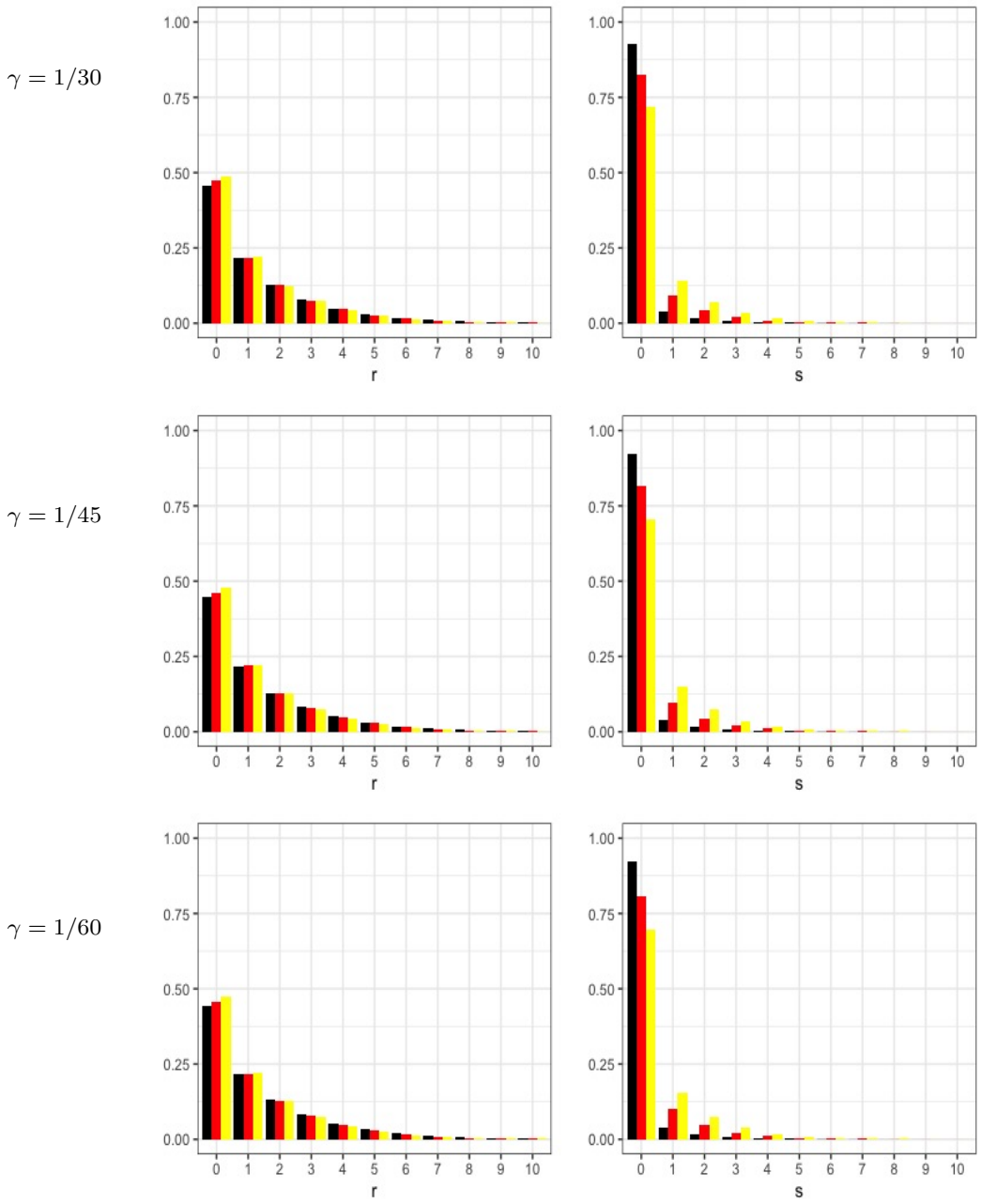

Figure 4: The mass functions $\{P(\mathcal{R}^R_{exact,0} = r|(S(0) + R(0), R(0)) = (1, 1)) : r \in \mathbf{N}_0\}$ (left column) and $\{P(\mathcal{R}^S_{exact,0} = s|(S(0) + R(0), R(0)) = (1, 1)) : s \in \mathbf{N}_0\}$ (right column) in scenarios with proportion $m = 0.2$ (black), 0.5 (red) and 0.8 (yellow), for values of $\mu^{-1} = 14$ *days*, $\gamma^{-1} \in \{30, 45, 60\}$ *days*, $\tau_1^{-1} = 5$ *days* and $\tau_2^{-1} = 10$ *days*.

of the sensitive strain will become more significant. A more frequent spontaneous clearance of bacterial carriage will also decrease the prevalence of both resistant and sensitive strains, although no very significant changes are observed in our numerical experiments in terms of expectations of $\mathcal{R}^R_{exact,0}$ and $\mathcal{R}^S_{exact,0}$.

Not surprisingly, the use of more effective drugs for which there is no resistance (i.e., increasing values of τ_2) will result in a reduction in the prevalence of both resistant and sensitive bacterial strains. More surprising, on at least first consideration, is the prediction that, at an early stage of the epidemic, the effectiveness of drug 1 will not necessarily result in a remarkable variation in the prevalence of resistant bacteria. More concretely, the model predicts that the use of less effective drugs for which there is resistance will lead to a more significant reduction in the prevalence of resistant bacteria only when more individuals already colonized with sensitive bacteria are admitted to the hospital.

A more detailed description of $\mathcal{R}^R_{exact,0}$ and of $\mathcal{R}^S_{exact,0}$ is displayed in Figure 4 (respectively, Figure 5) in terms of mass functions, instead of expected values, in selected scenarios with $m \in \{0.2, 0.5, 0.8\}$, for values of $\mu^{-1} = 14$ *days*, $\gamma^{-1} \in \{30, 45, 60\}$ *days*, $\tau_1^{-1} = 5$ *days* and $\tau_2^{-1} = 10$ *days* (respectively, $\tau_1^{-1} = 5$ *days*, $\tau_2^{-1} \in \{5, 10, 20\}$ *days*, $\mu^{-1} = 14$ *days* and $\gamma^{-1} = 30$ *days*). The random numbers $\mathcal{R}^R_{exact,0}$ and $\mathcal{R}^S_{exact,0}$ are seen to have unimodal distributions with a clear peak at points $r = 0$ and $s = 0$, meaning that events $\{\mathcal{R}^R_{exact,0} = 0\}$ and $\{\mathcal{R}^S_{exact,0} = 0\}$ occur more frequently than the others. This does not mean that the corresponding expectations of $\mathcal{R}^R_{exact,0}$ and $\mathcal{R}^S_{exact,0}$ are necessarily less than one, as shown in Figures 2 and 3. In our experiments, the tail of the distribution of $\mathcal{R}^R_{exact,0}$ is heavier than that of $\mathcal{R}^S_{exact,0}$, showing that the spread of the resistant strain appears to be more likely to occur than the spread of the sensitive one in an early stage of the epidemic. Despite this, the model predicts that $\mathcal{R}^R_{exact,0}$ will also take small values with high probability, just as $\mathcal{R}^S_{exact,0}$ will take large values with relatively significant, but small, probability.

5 Conclusions

In this work, we have developed a Markov chain version of the deterministic model for the spread of antibiotic-resistant bacteria in hospital settings proposed in [27]. We have focused our analysis on the exact number of secondary infections caused by all patients using a marked bed, which is initially occupied by an infected patient, until this bed is eventually occupied by a susceptible one. This stochastic descriptor allows one to estimate the "*infectivity of a bed*" in the ward, rather than of a single patient, by taking into account that patients arriving into the hospital ward can already be colonized with certain probability, and infect others. Our approach allows one to split the reproduction number into two random variables, depending on the type of infections caused (i.e., by either the antibiotic-sensitive or resistant bacterial strains), and to compute the joint probability distribution of these.

Our numerical results highlight the competition dynamics expected between the antibiotic-sensitive and antibiotic-resistant bacterial strains, which is directly related to the assumption of cross-immunity. Our results also show that the probability distributions of these

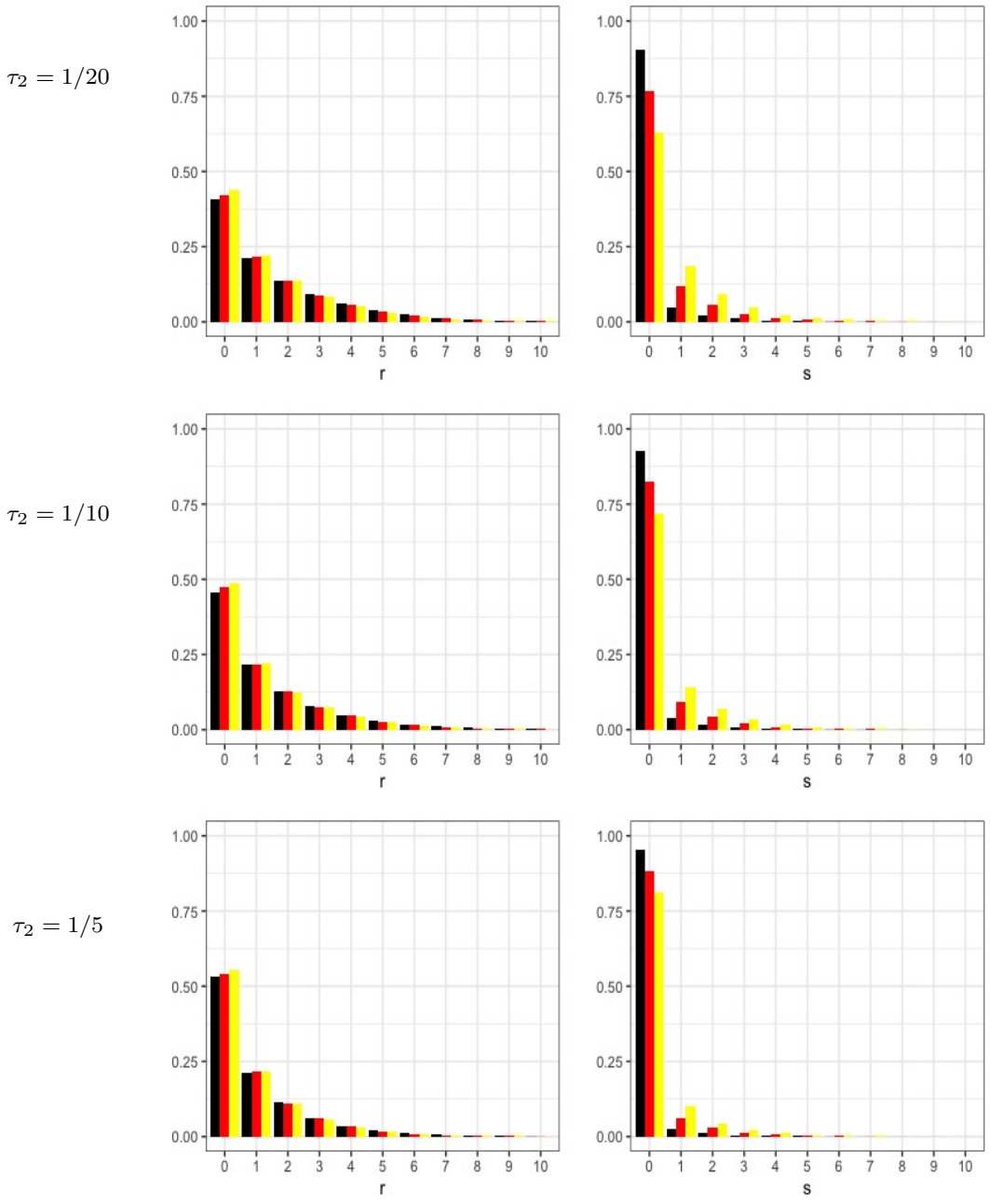

Figure 5: The mass functions $\{P(\mathcal{R}^R_{exact,0} = r|(S(0) + R(0), R(0)) = (1, 1)) : r \in \mathbf{N}_0\}$ (left column) and $\{P(\mathcal{R}^S_{exact,0} = s|(S(0) + R(0), R(0)) = (1, 1)) : s \in \mathbf{N}_0\}$ (right column) in scenarios with proportion $m = 0.2$ (black), 0.5 (red) and 0.8 (yellow), for values of $\tau_1^{-1} = 5$ *days*, $\tau_2^{-1} \in \{5, 10, 20\}$ *days*, $\mu^{-1} = 14$ *days* and $\gamma^{-1} = 30$ *days*.

exact reproduction numbers can, in fact, be very wide. Interestingly, one can find parameter regimes where the mean exact reproduction number is less than one, but there is a non-negligible probability of the marked bed causing a significant number of infections in early times, and regimes where the mean exact reproduction number is greater than one, but there is a significant probability of the marked bed causing zero infections. This could have a direct impact on the probability of an outbreak happening from a particular bed, and highlights the need to analyse these stochastic descriptors as random variables (i.e., in terms of probability distributions) rather than mean quantities.

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Conflict of interest

The authors declare no potential conflict of interests.

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A Expressions for matrices $\mathbf{B}_0$ and $\mathbf{C}_0(0)$ in Eq. (5)

From Eqs. (3)-(4) it is seen that $\mathbf{B}_0$ and $\mathbf{C}_0(0)$ are square matrices of order N and have the form

$$\mathbf{B}_0 = \begin{pmatrix} \frac{m\mu}{q_{(1,0)}} & \frac{(N-1)\beta}{q_{(1,0)}} & & & & \\ & \frac{m\mu}{q_{(2,0)}} & \frac{(N-2)\beta}{q_{(2,0)}} & & & \\ & & \ddots & \ddots & & \\ & & & \frac{m\mu}{q_{(N-1,0)}} & \frac{\beta}{q_{(N-1,0)}} & \\ & & & & \frac{m\mu}{q_{(N,0)}} & \end{pmatrix},$$

$$\mathbf{C}_0(0) = \begin{pmatrix} c'_{(1,0)} & c''_{(1,0)} & & & & \\ c_{(2,0)} & c'_{(2,0)} & c''_{(2,0)} & & & \\ & c_{(3,0)} & c'_{(3,0)} & c''_{(3,0)} & & \\ & & \ddots & \ddots & \ddots & \\ & & & c_{(N-1,0)} & c'_{(N-1,0)} & c''_{(N-1,0)} \end{pmatrix},$$

where $c_{(i,0)} = q^{-1}_{(i,0)}(i-1)(\gamma+\tau_1+\tau_2+(1-m)\mu)$, for $i \in \{2,...,N\}$, $c'_{(i,0)} = q^{-1}_{(i,0)}((N-i)(1-m)\mu+(i-1)m\mu)$, for $i \in \{1,...,N\}$, and $c''_{(i,0)} = q^{-1}_{(i,0)}(N-i)((i-1)\beta+m\mu)$, for $i \in \{1,...,N-1\}$.

B Expressions for matrices $\mathbf{B}_j$, $\mathbf{C}_j(0)$, $\mathbf{C}_{j-1}(1)$ and $\mathbf{C}_{j+1}(2)$ in Eq. (6)

In Eq. (6), $\mathbf{B}_j$ and $\mathbf{C}_j(0)$ are square matrices of order $N-j$, and matrices $\mathbf{C}_{j-1}(1)$ and $\mathbf{C}_{j+1}(2)$ are of dimension $(N-j)\times(N-j+1)$ and $(N-j)\times(N-j-1)$, respectively.

They are given by

$$\mathbf{B}_j = \begin{pmatrix} \frac{m\mu}{q_{(j+1,j)}} & \frac{(N-j-1)\beta}{q_{(j+1,j)}} & & & \\ & \frac{m\mu}{q_{(j+2,j)}} & \frac{(N-j-2)\beta}{q_{(j+2,j)}} & & \\ & & \ddots & \ddots & \\ & & & \frac{m\mu}{q_{(N-1,j)}} & \frac{\beta}{q_{(N-1,j)}} \\ & & & & \frac{m\mu}{q_{(N,j)}} \end{pmatrix},$$

$$\mathbf{C}_j(0) = \begin{pmatrix} c'_{(j+1,j)} & c''_{(j+1,j)} & & & & \\ c_{(j+2,j)} & c'_{(j+2,j)} & c''_{(j+2,j)} & & & \\ & c_{(j+3,j)} & c'_{(j+3,j)} & c''_{(j+3,j)} & & \\ & & \ddots & \ddots & \ddots & \\ & & & c_{(N-1,j)} & c'_{(N-1,j)} & c''_{(N-1,j)} \end{pmatrix},$$

$$\mathbf{C}_{j-1}(1) = \begin{pmatrix} \frac{j(\gamma+\tau_2+(1-m)\mu)}{q_{(j+1,j)}} & \frac{jm\mu}{q_{(j+1,j)}} & & & \\ & \frac{j(\gamma+\tau_2+(1-m)\mu)}{q_{(j+2,j)}} & \frac{jm\mu}{q_{(j+2,j)}} & & \\ & & \ddots & \ddots & \\ & & & \frac{j(\gamma+\tau_2+(1-m)\mu)}{q_{(N-1,j)}} & \frac{jm\mu}{q_{(N-1,j)}} \end{pmatrix},$$

$$\mathbf{C}_{j+1}(2) = \begin{pmatrix} \frac{(N-j-1)j(1-c)\beta}{q_{(j+1,j)}} & & & \\ & \frac{(N-j-2)j(1-c)\beta}{q_{(j+2,j)}} & & \\ & & \ddots & \\ & & & \frac{j(1-c)\beta}{q_{(N-1,j)}} \\ & & & 0 \end{pmatrix},$$

where $c_{(j+i,j)} = q^{-1}_{(j+i,j)}(i-1)(\gamma+\tau_1+\tau_2+(1-m)\mu)$, for $i \in \{2,...,N-j\}$, $c'_{(j+i,j)} = q^{-1}_{(j+i,j)}((N-j-i)(1-m)\mu+(i-1)m\mu)$, for $i \in \{1,...,N-j\}$, and $c''_{(j+i,j)} = q^{-1}_{(j+i,j)}(N-j-i)((i-1)\beta+m\mu)$, for $i \in \{1,...,N-j-1\}$.

C Expressions for matrices $\mathbf{E}_j$, $\mathbf{F}_j$, $\mathbf{D}_j(0)$, $\mathbf{D}_{j-1}(1)$ and $\mathbf{D}_{j+1}(2)$ in Theorems 2 and 3

Matrices $\mathbf{E}_j$, for $j \in \{1,...,N\}$, and $\mathbf{F}_j$, for $j \in \{1,...,N-1\}$, in Theorems 2 and 3 are of dimension $(N-j+1)\times(N-j+1)$ and $(N-j+1)\times(N-j)$, respectively, and are given

by

$$\mathbf{E}_j = \begin{pmatrix} \frac{m\mu}{q_{(j,j)}} & & & \\ & \frac{m\mu}{q_{(j+1,j)}} & & \\ & & \ddots & \\ & & & \frac{m\mu}{q_{(N,j)}} \end{pmatrix},$$

$$\mathbf{F}_j = \begin{pmatrix} \frac{(N-j)(1-c)\beta}{q_{(j,j)}} & & & \\ & \frac{(N-j-1)(1-c)\beta}{q_{(j+1,j)}} & & \\ & & \ddots & \\ & & & \frac{(1-c)\beta}{q_{(N-1,j)}} \\ & & & 0 \end{pmatrix}.$$

Matrices $\mathbf{D}_j(0)$, $\mathbf{D}_{j-1}(1)$ and $\mathbf{D}_{j+1}(2)$ are of dimension $(N-j+1)\times(N-j+1)$, $(N-j+1)\times(N-j+2)$ and $(N-j+1)\times(N-j)$, respectively, and have the form

$$\mathbf{D}_j(0) = \begin{pmatrix} d'_{(j,j)} & d''_{(j,j)} & & & & \\ d_{(j+1,j)} & d'_{(j+1,j)} & d''_{(j+1,j)} & & & \\ & d_{(j+2,j)} & d'_{(j+2,j)} & d''_{(j+2,j)} & & \\ & & \ddots & \ddots & \ddots & \\ & & & d_{(N-1,j)} & d'_{(N-1,j)} & d''_{(N-1,j)} \\ & & & & d_{(N,j)} & d'_{(N,j)} \end{pmatrix},$$

$$\mathbf{D}_{j-1}(1) = \begin{pmatrix} \frac{(j-1)(\gamma+\tau_2+(1-m)\mu)}{q_{(j,j)}} & \frac{(j-1)m\mu}{q_{(j,j)}} & & & \\ & \frac{(j-1)(\gamma+\tau_2+(1-m)\mu)}{q_{(j+1,j)}} & \frac{(j-1)m\mu}{q_{(j+1,j)}} & & \\ & & \ddots & \ddots & \\ & & & \frac{(j-1)(\gamma+\tau_2+(1-m)\mu)}{q_{(N,j)}} & \frac{(j-1)m\mu}{q_{(N,j)}} \end{pmatrix},$$

$$\mathbf{D}_{j+1}(2) = \begin{pmatrix} \frac{(N-j)(j-1)(1-c)\beta}{q_{(j,j)}} & & & \\ & \frac{(N-j-1)(j-1)(1-c)\beta}{q_{(j+1,j)}} & & \\ & & \ddots & \\ & & & \frac{(j-1)(1-c)\beta}{q_{(N-1,j)}} \\ & & & 0 \end{pmatrix},$$

where $d_{(j+i,j)} = q^{-1}_{(j+i,j)} i(\gamma+\tau_1+\tau_2+(1-m)\mu)$, for $i \in \{1,...,N-j\}$, $d'_{(j+i,j)} = q^{-1}_{(j+i,j)}((N-j-i)(1-m)\mu + im\mu)$, for $i \in \{0,...,N-j\}$, and $d''_{(j+i,j)} = q^{-1}_{(j+i,j)}(N-j-i)(i\beta+m\mu)$, for $i \in \{0,...,N-j-1\}$.