On network suppression of multidrug-resistant pathogen spread

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Abstract

In the paper we present a system of SIS type equations coupled by impulses at fixed times that describe the transfer of patients in the healthcare system represented by a graph of healthcare facilities and corresponding communities. The first aim for this considerations is to provide rigorous mathematical analysis of a general theoretical model, which is then used to model transmission of hospital acquired multi-drug resistant bacteria infections based on real patient hospital records provided by German insurance company – AOK Lower Saxony. Starting from the existence and the asymptotic behaviour, together with specification of parameter $\mathcal{R}_0$, we propose sufficient conditions guaranteeing network suppression of infection. Furthermore, conditions derived analytically and proposed numerical procedure are used to indicate healthcare facilities that are most prone to the high prevalence bacteria spread in the healthcare system and to ensure the stability of disease-free steady state of the system.

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1 Introduction

Description of a process that evolves continuously in time, excluding brief events that occur occasionally and break this trend, is a common challenge in applications. The first paper where the discontinuity was implemented in the form of a change of initial condition known as an impulse (in further considerations we refer to models of that kind as impulsive differential equation, IDE) is assigned to Milman and Myshkis[26]. The topic gained considerable interest resulting in a few monographs by Bainov et al.[4, 3, 5] or Lakshmikantham et al.[23] where systems of this kind are treated analytically. In the last decade however IDEs become widely used in applied sciences to describe e.g. cell differentiation[16], vaccinations' [46, 12], prey-predator systems' interactions[47, 45] or cancer growth and treatment [31, 20, 2, 9, 14] just to mention few of them.

Compared to the wide range of results in epidemiology where ODEs are applied, the literature in IDEs is more limited but still numerous. It is worth to divide them thematically into groups with respect to the kind of modelled pulse effect, namely impulse vaccinations[39, 40, 35], birth rate[18, 36], pest management[15, 44], quarantine[49], transfer between patches[11] etc.

In our approach we use impulse effect to describe the transfer of patients between healthcare facilities and communities, therefore the results are similar to those listed as the last approach. However, unlike Cordova–Lepe et al.[11], we focus on arbitrary relation between patients locations which makes the considerations more general, and similar to systems such as multigroup ODEs[41] or multigroup McKendrick type models[22, 48]. Moreover, presented study is an attempt to understand the dynamics of deterministic computational models proposed earlier[32, 34] and to analyse it in rigorous mathematical way.

This paper is organized as follows. In Section 2 a family of multigroup SIS type modes is introduced. Next, in Section 3 we prove basic mathematical properties of the considered system – the global existence and nonnegativity of the solutions. This considerations are followed in Section 4 by investigation of the long-time behaviour of the solutions including: existence of steady states, study of local stability of disease-free steady state and existence of τ-periodic solutions. Additionally, in Subsection 4.2 we prove several propositions, derived from network structure perspective, allowing to achieve the stability of the disease-free steady state. Finally, we focus on the particular computational models[34, 32] and show that our analytical considerations can be used to propose effective countermeasure reducing the system-wide prevalence of multidrug-resistant bacteriae (such as *Escherichia coli* and *Klebsiella pneumoniae*) in the healthcare system.

2 Model description

In this paragraph we build a mathematical background that allows us to rigorously describe a transmission of a pathogen such as multidrug-resistant bacteriae (MDR) in the human

population understood as transmission of bacteriae between groups of patients that visit certain healthcare facilities with a certain frequency. Considered healthcare network consists of n healthcare facilities (later called *H-nodes*, indexed over $J_n = \{1, \ldots, n\}$) and n corresponding communities (later called *C-nodes*, indexed over $\bar{J}_n = \{n+1, \ldots, 2n\}$). For brevity, by a *HC-pair* we denote a pair of healthcare facility with a corresponding community node. Let $\mathcal{H}(t) = (H_i(t))_{i \in J_{2n}}^T$, where $J_{2n} = \{1, \ldots, 2n\}$ and $H_i(t)$ denotes a fraction of all individuals staying at i-th healthcare facility for $i \in J_n$, or at i-th community for $i \in \bar{J}_n$, at given time $t \geq 0$. In particular, the i-th community consists of individuals whose recent hospitalisation took place in $i-n$-th healthcare facility.

Let us divide each of $2n$-groups of patients into susceptible and infectious subpopulations, resp. $S_i(t)$ and $I_i(t)$, $i \in J_{2n}$. Then,

$$S_i(t) + I_i(t) = H_i(t) \quad \text{and} \quad \sum_{i \in J_{2n}} H_i(t) = 1. \tag{1}$$

In addition, denote $\mathcal{S}(t) = (S_i(t))_{i \in J_{2n}}^T$ and $\mathcal{I}(t) = (I_i(t))_{i \in J_{2n}}^T$.

We assume that individuals are not aware of being infectious, thus the process of relocation of patients from both groups is described by the same transfer matrix $\mathcal{K} = (k_{ij})_{i,j \in J_{2n}} \in M_{2n \times 2n}([0,1])$, where $M_{2n \times 2n}([0,1])$ denotes $2n \times 2n$ matrix with elements from the interval $[0,1]$. Individuals stay in one location for time $\tau > 0$, which in case of our numerical simulations equals to 1 day, next they are either transferred or stay in the same place (meaning in healthcare facility or community) for the next time period τ. Coefficients k_{ij} can be interpreted in the following way. If $j \in J_n$ then k_{ij} is probability of: transfer of individuals from j-th healthcare facility to i-th healthcare facility (for $i \in J_n$, $i \neq j$); stay in j-th hospital overnight (for $i \in J_n$, $i = j$) or discharge from the j-th healthcare facility i.e. to i-th community (for $i \in \bar{J}_n$). Analogously for $j \in \bar{J}_n$ k_{ij} is probability of admission of individuals from j-th community to i-th healthcare facility (for $i \in J_n$); move to i-th community (for $i \in \bar{J}_n$, $i \neq j$) or stay in j-th community (for $i \in \bar{J}_n$, $i = j$).

Following Piotrowska et al.[34, 32], in numerical simulations, we additionally assume that i-th medical facility discharges its patients to $i+n$-th community, and that movements between communities are not allowed, hence for $i \in \bar{J}_n$

$$k_{ij} \neq 0 \quad \text{if and only if} \quad (i,j) = (i,i) \text{ or } (i,j) = (i, i+n). \tag{2}$$

In earlier, computationally based, approaches[32, 34] this assumption is required for two reasons. First to "track" the history of patients in the sense of the knowledge of the previous hospitalization and second to consider in the model only the hospitalized people instead of the whole society. Clearly, under such assumptions communities in models proposed by Piotrowska et al.[32, 34] do not represent real communities in the society, but rather are "containers" of patients who have left particular hospital and whose households might not be

even geographically close to each other. Nevertheless, to make our analytical considerations more general in the following we only assume that $\mathcal{K}$ is column stochastic matrix, namely the entries are nonnegative and in columns they sum up to 1.

Finally, we assume that the transmission of infections is governed by a SIS-type (susceptible-infectious-susceptible) model[24, 22]. Define $\Gamma = \mathrm{diag}(\gamma_i)_{i\in J_{2n}}$, where $\gamma_i > 0$ denotes patient recovery rate in a given healthcare facility for $i \in J_n$ and at community for $i \in \bar{J}_n$. In addition let $\mathbf{B} = \mathrm{diag}(\beta_i)_{i\in J_{2n}}$, such that for $i \in J_n$ parameter $\beta_i > 0$ is a transmission rate at i-th healthcare facility, while for $i \in \bar{J}_n$ parameter $\beta_i \geq 0$ indicates a possible lack of further transmission of infection at community.

Following the approach of impulsive systems at fixed times, we define continuous dynamical system describing the spread of infection on each time interval $(k\tau, (k+1)\tau)$, $k \in \mathbb{N} \cup \{0\}$. Clearly, due to the impulse nature of the model we do not expect the solution to be continuous. Instead, we use the space of piecewise continuous functions with discontinuity of a first kind, denoted by $PC([0,\infty))$, endowed with supremum norm, to model the process. Moreover, in the following we use a notation of Hadamard product

$$\mathcal{I} \circ \mathcal{S} = (I_i S_i)_{i\in J_{2n}}^T . \tag{3}$$

Abusing a notation, let $\mathcal{H}^{-1}(t) := (1/H_i(t))_{i\in J_{2n}}$. Well-posedness and positivity of the mathematical formulation is explained in Theorem 1. It agrees also with the intuition that comes from applications that starting from a nonzero fraction of individuals in the strongly connected network, there are always patients in each node. We formulate network multigroup SIS type model with impulses to be considered in this paper as follows:

$$\left.\begin{array}{rcl} \dot{\mathcal{S}}(t) &=& -\mathbf{B}(\mathcal{I}\circ\mathcal{S}\circ\mathcal{H}^{-1})(t) + \Gamma\mathcal{I}(t) \\ \dot{\mathcal{I}}(t) &=& \mathbf{B}(\mathcal{I}\circ\mathcal{S}\circ\mathcal{H}^{-1})(t) - \Gamma\mathcal{I}(t) \end{array}\right\} t \in (k\tau,(k+1)\tau],\ k \in \mathbb{N}\cup\{0\}$$
$$\left.\begin{array}{rcl} \mathcal{S}(t^+) &=& \mathcal{K}\mathcal{S}(t), \\ \mathcal{I}(t^+) &=& \mathcal{K}\mathcal{I}(t), \end{array}\right\} t = k\tau,\ k \in \mathbb{N} \tag{4}$$
$$\mathcal{S}(0^+) = \mathcal{S}_0 \in [0,1]^{2n}, \quad \mathcal{I}(0^+) = \mathcal{I}_0 \in [0,1]^{2n}, \quad \mathcal{H}_0 \in (0,1]^{2n}.$$

Finally, we relate the structure of patients' transfers between healthcare facilities and between healthcare facilities and communities with a directed and weighted graph $G = (V, E, \omega)$ such that nodes $V = \{v_i : i \in J_{2n}\}$ represent healthcare facilities and corresponding communities and edges E inform about the possibility of transfer. For simplicity of notation we refer to the elements of sets $\{v_i : i \in J_n\}$ and $\{v_i : i \in \bar{J}_n\}$ as H-nodes and C-nodes, respectively. In numerical simulations, when condition (2) holds, elements of $\{(v_i, v_{i+n}) : i \in J_n\}$ are called HC-pairs. If there exists an edge e such that has a head in v_j and a tail in v_i (we write respectively $e^{term} = v_j$ and $e^{init} = v_i$), for some $i, j \in J_{2n}$ then the transfer from v_i to v_j is possible. Weights

of edges are represented by function $\omega : E \to [0,1]$ such that for any $e \in E$

$$\omega(e) = k_{ji}, \qquad \text{if} \quad e^{init} = v_i \ \text{ and } \ e^{term} = v_j.$$

The weight of an edge therefore gives a probability of patients' transfer between two healthcare facilities/communities associated respectively with a tail and a head of an edge.

Finally it is worth mentioning that if $\mathcal{K}$ is an adjacency matrix of some arbitrary line graph, see Beineke and Wilson[8] p. 8 for definition, then the problem is graph realisable[6]. It can be then considered as a transfer of patients along the edges of a metric graph[28]. For other models of that kind we refer reader to Kramar-Fijavž and Puchalska[21].

3 Well-possedness of the model

In the following consideration we denote by $r(\mathcal{K}), \sigma(\mathcal{K})$ the spectral radius and spectrum of $\mathcal{K}$, respectively. Let $\mathcal{P}_1 : \mathbb{R}^{2n} \to \ker(\mathcal{K} - \mathrm{Id})$ be a projection onto $\ker(\mathcal{K} - \mathrm{Id})$ along $\mathrm{im}\,(\mathcal{K} - \mathrm{Id})$, with $\mathrm{Id} \in M_{2n\times 2n}([0,1])$ being an identity matrix. For column stochastic matrix $\mathcal{K}$, $r(\mathcal{K}) = 1$ (see Sec. 8.4, page. 489 in book by Meyer[25]) and by *Perron-Frobenius theorem*, a right eigenvector of $\mathcal{K}$ associated with $r(\mathcal{K}) \in \sigma(\mathcal{K})$ is nonnegative and by $\mathcal{H}_\infty$ we denote its normalised representative $\|\mathcal{H}_\infty\|_1 = \sum_{i\in J_{2n}} (\mathcal{H}_\infty)_i = 1$. The projection $\mathcal{P}_1$ can be expressed explicitly by

$$\mathcal{P}_1 x = \sum_{i\in J_{2n}} x_i \, \mathcal{H}_\infty, \qquad \text{for any } x \in \mathbb{R}^{2n}. \tag{5}$$

3.1 The total sub-populations

In the following we describe a long-time behaviour of a total sub-population of patients at each node. Clearly, it satisfies the following impulsive system

$$\begin{aligned} &\dot{\mathcal{H}}(t) = 0 && t \in (k\tau, (k+1)\tau]\,,\ k \in \mathbb{N}\cup\{0\} \\ &\mathcal{H}(t^+) = \mathcal{K}\mathcal{H}(t) && t = k\tau,\ k \in \mathbb{N} \\ &\mathcal{H}(0^+) = \mathcal{H}_0 \in [0,1]^{2n}, \end{aligned} \tag{6}$$

with $\mathcal{H}_0 := \mathcal{S}_0 + \mathcal{I}_0$.

Lemma 1. *For any column stochastic matrix $\mathcal{K}$ there exist a unique solution to system* (6) *of a form*

$$\mathcal{H}(t) = \mathcal{K}^k \mathcal{H}_0, \qquad \textit{for any} \quad t \in (k\tau, (k+1)\tau]\,,\ k \in \mathbb{N}\cup\{0\}\,, \tag{7}$$

and $\mathcal{H}(0) = \mathcal{H}_0$. If $\mathcal{K}$ is additionally irreducible and primitive matrix, then vector of patient sub-populations converges to $\mathcal{H}_\infty$.

Proof. The solution of (6) is constant at each interval and by the explicit formula for linear recursion we have

$$\begin{aligned} \mathcal{H}(t) &= \mathcal{H}_0 \text{ for } t \in [0, \tau] \\ \mathcal{H}(t) &= \mathcal{H}_k \text{ for } t \in (k\tau, (k+1)\tau],\ k \in \mathbb{N}, \end{aligned} \tag{8}$$

where $\mathcal{H}_k := \mathcal{K}^k \mathcal{H}_0$, which yields (7). It is clear that $r(\mathcal{K}) = 1 \in \sigma(\mathcal{K})$, since $\mathcal{K}$ is column stochastic.

If $\mathcal{K}$ is additionally irreducible, then multiplicity of $r(\mathcal{K})$ is one; see Thm. 5.13 in Bátkai et al.[7]. Assumption that $\mathcal{K}$ is primitive imply that $\lambda = 1$ is dominant eigenvalue, by Def. 5.17 in Bátkai et al.[7]. Hence, from Cor. 5.16 in Bátkai et al.[7], by the form of projection (5) and assumption (1) we obtain the thesis. □

Let us elaborate on the result of Proposition 1 in the context of healthcare network and transfers between community and healthcare facilities. The crucial information is hidden in the mapping $\mathcal{P}_1$. It projects the dynamics considered in every node into the subspace of vertices adjacent to edges in so-called terminal-strong component of a network G (see page 19 in Bang-Jensen and Gutin[19] for a definition). By *active nodes* we denote the H- and C-nodes from a set V_0 defined as

$$V_0 := \{v_i \in V :\ i \in J_{2n},\ (\mathcal{H}_\infty)_i \neq 0\}, \tag{9}$$

and by

$$J_0 := \{i \in J_{2n} :\ v_i \in V_0\}. \tag{10}$$

a set of indexes of *active nodes*. Definition of $\mathcal{H}_\infty$ implies that only active nodes have real impact on the dynamics of the considered healthcare network since all patients are finally occupying only this units. This observation justifies the numerical procedure proposed by Piotrowska et al.[32, 34], where only healthcare facilities contained in V_0 are taken into account.

Note that irreducibility of positive matrix $\mathcal{K}$ is equivalent to strong connectedness of a graph G, see Thm. IV.3.2 in the book by Minc[27]. Define now adjacency matrix $\bar{\mathcal{K}} = (\bar{k}_{ij})_{i,j \in J_{2n}}$ of graph G as follows

$$\bar{k}_{ij} = \begin{cases} 1 & \text{if } k_{ij} \neq 0, \\ 0 & \text{otherwise.} \end{cases}$$

Let us remind that (i, j)-th element of m-th power of adjacency matrix $\bar{\mathcal{K}}$ gives a number of paths of the length m from the node v_j to v_i, see Thm. IV.3.1 in the book by Minc[27]. Therefore strong connectedness of a network is equivalent to condition

$$\forall_{i,j \in J_{2n}}\ \exists_{m \in \mathbb{N}} \quad \bar{\mathcal{K}}^m_{ij} > 0,$$

where $\bar{\mathcal{K}}^m_{ij}$ denotes the (i,j)-th element of $\bar{\mathcal{K}}^m$ matrix, see Cor. IV.3.1 in the book by Minc[27]. If the order of quantifiers can be reversed then the matrix $\mathcal{K}$ is primitive, compare Lem. IV.3.1 in the book by Minc[27]. Therefore, we can interpret the primitivity of matrices in the context of the prevalence of resistant pathogens in hospital-community system in the following way. There exists a moment in time $t = m\tau$ when a total sub-population of patients in each node is affected directly by *any* considered node. Such a situation does not take place for instance when graph has a cyclic structure (since then the total sub-population is always affected only by a certain number of facilities that are the neighbours in the cycle). We take a special care to identify such cases, as they are unrealistic and if they are present in the model, they indicate possible error in data analysis or other types of inaccuracy.

3.2 Existence of solutions

Using the explicit formula for $\mathcal{H}$ given in (8) we transform the original model (4) into $2n$-dimensional one obtaining

$$\begin{aligned} \dot{\mathcal{I}}(t) &= -\mathbf{B}(\mathcal{I}\circ\mathcal{I}\circ\mathcal{H}_k^{-1})(t) + (\mathbf{B}-\Gamma)\mathcal{I}(t) && t\in(k\tau,(k+1)\tau]\ k\in\mathbb{N}\cup\{0\} \\ \mathcal{I}(t^+) &= \mathcal{K}\mathcal{I}(t) && t=k\tau,\ k\in\mathbb{N} \\ \mathcal{I}(0^+) &= \mathcal{I}_0\in[0,1]^{2n}. \end{aligned} \tag{11}$$

Note that for $t\in(k\tau,(k+1)\tau]$, $k\in\mathbb{N}$, at each coordinate $i\in J_{2n}$ the equation simplifies to the scalar logistic equation, namely

$$\begin{aligned} \dot{I}_i(t) &= -\tfrac{\beta_i}{(\mathcal{H}_k)_i}I_i^2(t) + (\beta_i-\gamma_i)I_i(t), \\ I_i(k\tau) &= I_i(k\tau^+). \end{aligned} \tag{12}$$

Consider now functions $a(k,t) = (a_i(k,t))_{i\in J_{2n}}$ and $b(k,t) = (b_i(k,t))_{i\in J_{2n}}$ for $k\in\mathbb{N}\cup\{0\}$ and $t\in(k\tau,(k+1)\tau]$ such that for $i\in J_{2n}$ the following holds

$$a_i(k,t) = e^{(\beta_i-\gamma_i)(t-k\tau)}, \tag{13}$$

$$b_i(k,t) = \begin{cases} \frac{\beta_i}{(\beta_i-\gamma_i)(\mathcal{H}_k)_i}(a_i(k,t)-1) & \text{for } \beta_i\neq\gamma_i, \\ \frac{\beta_i}{(\mathcal{H}_k)_i}(t-k\tau) & \text{for } \beta_i=\gamma_i. \end{cases} \tag{14}$$

Note that functions (13) and (14) are positive, where the positivity of the second term in the case of $\beta_i\neq\gamma_i$ follows from the positivity of $\frac{a_i(k,t)-1}{\beta_i-\gamma_i}$. Furthermore, define

$$a := (a_i(k,(k+1)\tau))_{i\in J_{2n}} \quad\text{and}\quad \mathcal{A} := \operatorname{diag}(a)\in M_{2n\times 2n}(0,\infty) \tag{15}$$

which, by (13), are both independent of k. The solution of (12) for $t\in(k\tau,(k+1)\tau]$ and $i\in J_{2n}$

is given by nonlinear operator $T_i(k,t) : [0,1] \to PC((k\tau,(k+1)\tau])$ such that

$$T_i(k,t)\left(I_i(k\tau^+)\right) = \frac{a_i(k,t)I_i(k\tau^+)}{1+\ b_i(k,t)I_i(k\tau^+)}. \tag{16}$$

Note also that if $\beta_i = 0$, then $T_i(k,t)$ becomes linear, namely $T_i(k,t)\left(I_i(k\tau^+)\right) = a_i(k,t)I_i(k\tau^+)$.

Theorem 1. *For any $\mathcal{I}_0 \in [0,1]^{2n}$ there exists a unique, nonnegative solution of (11), that remains in $[0,1]^{2n}$, which depends continuously on initial condition for $t \neq k\tau$, $k \in \mathbb{N}\cup\{0\}$, such that for $t \in (k\tau,(k+1)\tau]$, $k \in \mathbb{N}\cup\{0\}$*

$$\mathcal{I}(t) = T(k,t-k\tau)\,\Pi_{j=1}^{k}\mathcal{K}T(k-j,\tau)(\mathcal{I}_0)\,, \tag{17}$$

where each coordinate of $T(k,t) = (T_i(k,t))_{i=1,\ldots,2n}$ is given by (16) and Π should be understood as composition of operators. Furthermore the solution is positive for any $\mathcal{I}_0 \in (0,1]^{2n}$.

Proof. Existence and uniqueness of a local solution follows from Thm. 1.2.2 and Cor. 2.2.1 in Lakshmikantham et al.[23]. An explicit formula for a solution is proved by induction and nonnegativity is a consequence of nonnegativity of oparators $T(k,t)$ and $\mathcal{K}$. A global existence of nonnegative solution follows from Thm. 1.4.4 in Lakshmikantham et al.[23] and the following estimate

$$\begin{array}{lcll} \dot{\mathcal{I}}(t) & \leq & (\mathbf{B}-\Gamma)\,\mathcal{I}(t), & t \neq k\tau, \\ \mathcal{I}(t^+) & \leq & \mathcal{K}\mathcal{I}(t), & t = k\tau, \\ \mathcal{I}(0) & = & \mathcal{I}_0 \in (0,1]^{2n}. & \end{array} \tag{18}$$

Continuous dependence on initial condition for any $t \neq k\tau$, $k \in \mathbb{N}$ is based on Thm. 2.3.1 in Lakshmikantham et al.[23].

To show the positivity of solutions note that for $i \in J_{2n}$, $\mathcal{I}_i(k\tau^+) \geq 0$, $\mathcal{I}_i$ is an increasing function and attains 0 only for $\mathcal{I}_i(k\tau^+) = 0$. If the solution $\mathcal{I}$ of (11) is not positive then for $\mathcal{I}_0 > 0$, the first argument $t_0 > 0$ such that $\mathcal{I}(t_0) = 0$ is of a form $t_0 = k_0\tau^+$, $k_0 \in \mathbb{N}$. On the other hand,

$$\mathcal{I}(k_0\tau^+) = \mathcal{K}\mathcal{I}(k_0\tau) = 0,$$

holds leading to contradiction since $\mathcal{K}$ as nontrivial, and nonnegative matrix cannot have a positive eigenvector $\mathcal{I}(k_0\tau)$ corresponding to zero eigenvalue.

Finally, since $\mathcal{K}$ is stochastic and $\dot{\mathcal{H}} = 0$ the system (11) is conservative. Therefore by (1) $\sup_{t\in[0,\infty)}\mathcal{I}(t) \leq 1$. □

4 Long-time behaviour

The considerations in this section are devoted to irreducible and primitive matrix $\mathcal{K}$. To simplify a notation let

$$b := \lim_{k\to\infty} b(k,(k+1)\tau), \tag{19}$$

which by (14) and Proposition 1 is well posed, and define function $\mathcal{F} : (0,\infty)^{2n} \to (0,\infty)^{2n}$ as follows

$$\mathcal{F}(\mathcal{I}) = \left(\frac{a_i I_i}{1+b_i I_i}\right)_{i\in J_{2n}}. \tag{20}$$

4.1 Steady states and τ-periodic solutions

First we focus on the existence of disease free and endemic steady states. For that purpose define the following constants

$$\mathcal{R}_0 := r(\mathcal{K}\mathcal{A}), \tag{21}$$

$$\mathcal{R}_1 := \min_{i\in J_0}\left(\frac{\beta_i}{\gamma_i}\right), \tag{22}$$

with a set of indices J_0 defined in (10). Moreover, we say that system (11) satisfies condition $(*)$ if

$$\text{there exist a constant } l>1 \text{ such that for any } i\in J_{2n}\ \beta_i = l\gamma_i. \tag{$*$}$$

We also note easily that condition $(*)$ implies that $\mathcal{R}_1 > 1$.

Clearly, matrix $\mathcal{K}\mathcal{A}$ is the next generation matrix known from the literature[42, 43]. Its (i,j)-th element is the expected number of new (secondary) infections in compartment i consisting of completely susceptible population, produced by the infected (colonized) individual originally introduced into compartment j, while $\mathcal{R}_0$ is called *basic reproduction number*[13, 42].

Lemma 2. *Let $\mathcal{K}$ be a primitive and irreducible matrix. Independently on the model parameters, there always exists a disease free steady state of system* (11)*. If $\mathcal{R}_1 \le 1$, then it is the only nonnegative steady state of the system. Furthermore, if $\mathcal{R}_1 > 1$ and $(*)$ holds, then there exists also endemic steady state given by*

$$\mathcal{I}^* = \left(1-\frac{1}{l}\right)\mathcal{H}_\infty, \tag{23}$$

where $\mathcal{H}_\infty$ is normalised nonnegative representative of right eigenvector of $\mathcal{K}$ associated with $r(\mathcal{K}) \in \sigma(\mathcal{K})$.

Proof. By definition, a disease free steady state of system (11) exists independently on the parameter values. Note that if there exist other fixed point $\mathcal{I}^* = (\mathcal{I}_i^*)_{i\in J_{2n}}$ then $\mathcal{F}(\mathcal{I}^*) = \mathcal{I}^*$ and

thus

$$I_i^* = \left(1 - \frac{\gamma_i}{\beta_i}\right)(\mathcal{H}_\infty)_i = \left(1 - \frac{1}{l}\right)(\mathcal{H}_\infty)_i, \quad \text{for } i \in J_{2n}.$$

Its positivity is guaranteed by the condition $\mathcal{R}_1 > 1$, and additionally we have $\mathcal{I}^* \in \ker(\mathcal{K} - Id) = \operatorname{span}\{\mathcal{H}_\infty\}$. Finally, $\mathcal{I}^*$ is a nontrivial nonnegative fixed point because $l > 1$. □

Lemma 3. *Let $\mathcal{K}$ be a primitive and irreducible matrix. The disease free steady state of system* (11) *is locally asymptotically stable for $\mathcal{R}_0 < 1$, while for $\mathcal{R}_0 > 1$ it is unstable.*

Proof. To examine local stability of disease free steady state we linearise a problem at zero obtaining

$$(\mathcal{K}\mathcal{F})'(0) = \mathcal{K}\mathcal{A},$$

so if $\mathcal{R}_0 < 1$, then zero is locally asymptotically stable while for $\mathcal{R}_0 > 1$ it is unstable. □

Now let us focus on the characterisation of possible periodic behaviour of the considered system. Let $j_0 := \#\{i \in J_{2n} : \ \beta_i = 0\}$ and without loss of generality assume that $\beta_i = 0$ for $i \in \bar{J}_{2n-j_0} := \{2n - j_0 + 1, \ldots, 2n\}$. Thus, we specify a new partition of a set $J_{2n} = J_{2n-j_0} \cup \bar{J}_{2n-j_0}$ and divide operator $\mathcal{K}$ into a block matrices. Namely let $\mathcal{K} = (\hat{\mathcal{K}}_{ij})_{i,j=1,2}$ such that $\hat{\mathcal{K}}_{11} \in M_{(2n-j_0)\times(2n-j_0)}([0,1]), \hat{\mathcal{K}}_{22} \in M_{j_0\times j_0}([0,1])$ and $\hat{\mathcal{K}}_{12}, \hat{\mathcal{K}}_{21}^T \in M_{2n-j_0\times j_0}([0,1])$. Moreover, we use a hat to define any $2n$-dimensional vector divided according to new index permutation, for example let $\mathcal{I} = (\hat{\mathcal{I}}_1, \hat{\mathcal{I}}_2)$, $\hat{\mathcal{I}}_1 = (I_i)_{i\in J_{2n-j_0}}$ and $\hat{\mathcal{I}}_2 = (I_i)_{i\in \bar{J}_{2n-j_0}}$. Additionally, for a given in (15) and $i = 1, 2$ we define

$$\hat{\mathcal{A}}_i := \operatorname{diag}(\hat{a}_i), \quad \text{where} \quad \hat{a}_1 = (a_i)_{i\in J_{2n-j_0}}, \ \hat{a}_2 = (a_i)_{i\in \bar{J}_{2n-j_0}}. \tag{24}$$

If we additionally assume that for $j_0 > 0$ matrix $(\mathrm{Id} - \hat{\mathcal{K}}_{22}\hat{\mathcal{A}}_2)$ is invertible, then we specify parameter which relates the rate of spread of infection with the structure of a graph in the following way

$$\mathcal{R} := \min_{i\in J_{2n-j_0}} s_i, \tag{25}$$

where

$$s_i := (\mathcal{K}a)_i \quad \text{for} \quad \bar{J}_{2n-j_0} = \emptyset \tag{26}$$

and

$$s_i := \left(\hat{\mathcal{K}}_{11}\hat{a}_1 + \hat{\mathcal{K}}_{12}\hat{\mathcal{A}}_2(\mathrm{Id} - \hat{\mathcal{K}}_{22}\hat{\mathcal{A}}_2)^{-1}\hat{\mathcal{K}}_{21}\hat{a}_1\right)_i \text{ otherwise.} \tag{27}$$

Theorem 2. *Let $\mathcal{K}$ be a primitive and irreducible matrix such that $(\mathrm{Id} - \hat{\mathcal{K}}_{22}\hat{\mathcal{A}}_2)$ is invertible. If $\mathcal{R} > 1$ system* (11) *has a nonnegative τ-periodic endemic solution $\mathcal{I}^*(t)$. Furthermore, if*

condition $(*)$ *holds, then* τ*-periodic solution becomes a nonegative endemic steady state defined in* (23).

Proof. For the sake of convenience, within this proof we define functions $\hat{\mathcal{F}}_1, \hat{\mathcal{Z}}_1 : (0,\infty)^{2n-j_0} \to (0,\infty)^{2n-j_0}$ and $\hat{\mathcal{F}}_2, \hat{\mathcal{Z}}_2 : (0,\infty)^{j_0} \to (0,\infty)^{j_0}$, which according to the new indices permutation, for $j = 1, 2$, are given by

$$\hat{\mathcal{F}}_j(\hat{\mathcal{I}}_j) = (F_i(I_i))_{i\in x}\,, \quad \text{and} \quad \hat{\mathcal{Z}}_j(\hat{\mathcal{I}}_j) = (Z_i(I_i))_{i\in x}\,,$$

where $x = J_{2n-j_0}$ for $j = 1$ and $x = \bar{J}_{2n-j_0}$ for $j = 2$; while

$$F_i(I) = \frac{a_i I}{1+b_i I} \quad \text{and} \quad Z_i(I) = \frac{I}{1+b_i I}. \tag{28}$$

We note that $(\hat{\mathcal{F}}_1(\hat{\mathcal{I}}_1), \hat{\mathcal{F}}_2(\hat{\mathcal{I}}_2))^T = (\hat{\mathcal{A}}_1\hat{\mathcal{Z}}_1(\hat{\mathcal{I}}_1), \hat{\mathcal{A}}_2\hat{\mathcal{Z}}_2(\hat{\mathcal{I}}_2))^T$.

First, consider $\bar{J}_{2n-j_0} \neq \emptyset$. A nontrivial τ-periodic solution $\mathcal{I}^*(t)$ satisfies condition $\mathcal{K}\mathcal{F}(\mathcal{I}) = \mathcal{I}$, which expands to

$$\hat{\mathcal{K}}_{11}\hat{\mathcal{A}}_1\hat{\mathcal{Z}}_1(\hat{\mathcal{I}}_1) + \hat{\mathcal{K}}_{12}\hat{\mathcal{A}}_2\hat{\mathcal{I}}_2 = \hat{\mathcal{I}}_1, \tag{29}$$

$$\hat{\mathcal{K}}_{21}\hat{\mathcal{A}}_1\hat{\mathcal{Z}}_1(\hat{\mathcal{I}}_1) + \hat{\mathcal{K}}_{22}\hat{\mathcal{A}}_2\hat{\mathcal{I}}_2 = \hat{\mathcal{I}}_2. \tag{30}$$

Since matrix $(\mathrm{Id} - \hat{\mathcal{K}}_{22}\hat{\mathcal{A}}_2)$ is invertible, we rewrite (30) as follows

$$\hat{\mathcal{I}}_2 = \left(\mathrm{Id} - \hat{\mathcal{K}}_{22}\hat{\mathcal{A}}_2\right)^{-1}\hat{\mathcal{K}}_{21}\hat{\mathcal{A}}_1\hat{\mathcal{Z}}_1(\hat{\mathcal{I}}_1). \tag{31}$$

Plugging (31) into (29) we transform the considered fixed point problem into $\hat{\mathcal{K}}\hat{\mathcal{F}}_1\left(\hat{\mathcal{I}}_1\right) = \hat{\mathcal{I}}_1$ with $\hat{\mathcal{K}} = (\hat{k}_{ij})_{i,j\in J_{2n-j_0}}$ as follows

$$\hat{\mathcal{K}} = \hat{\mathcal{K}}_{11} + \hat{\mathcal{K}}_{12}\hat{\mathcal{A}}_2\left(\mathrm{Id} - \hat{\mathcal{K}}_{22}\hat{\mathcal{A}}_2\right)^{-1}\hat{\mathcal{K}}_{21}. \tag{32}$$

Since Z_i is invertible for any $i \in J_{2n-j_0}$ except of b_i^{-1}, we have $\hat{\mathcal{Z}}_1^{-1} : \prod_{i\in J_{2n-j_0}}[0, b_i^{-1}) \to [0,\infty)^{2n-j_0}$, $\hat{\mathcal{Z}}_1^{-1}(\hat{\mathcal{Y}}_1) = \left(Z_i^{-1}(Y_i)\right)_{i\in J_{2n-j_0}}$ with $\hat{\mathcal{Y}}_1 = (Y_i)_{i\in J_{2n-j_0}}$ defined by

$$Z_i^{-1}(Y) = \left(\frac{Y}{1-b_i Y}\right)_{i\in J_{2n-j_0}}.$$

In further considerations we also use $G_i : [1,\infty) \to [0, b_i^{-1})$ and its inverse $G_i^{-1} : [0, b_i^{-1}) \to [1,\infty)$, for $i \in J_{2n-j_0}$ such that

$$G_i(Y) = \frac{Y-1}{b_i Y} \quad \text{and} \quad G_i^{-1}(Y) = \frac{1}{1-b_i Y}.$$

Define now

$$c := \min_{i\in J_{2n-j_0}} G_i(s_i) \quad \text{and} \quad C := \max_{i\in J_{2n-j_0}} \left\{ G_i(s_i) :\ G_i(s_i) < \min_{s\in J_{2n-j_0}} b_s^{-1} \right\}.$$

For $\mathcal{R} > 1$ we have $c > 0$ and maximum is chosen from nonempty set. Definition of s_i in (27) implies that $1 \le G_i^{-1}(c) \le s_i \le G_i^{-1}(C)$. Thus, for $i \in J_{2n-j_0}$,

$$Z_i^{-1}(c) = c\, G_i^{-1}(c) \le c\, s_i \le\ C\, s_i \le C\, G_i^{-1}(C) = Z_i^{-1}(C). \tag{33}$$

Finally choosing $K := \prod_{i=1}^{2n-j_0} [m_i, M_i]$ with

$$m_i := Z_i^{-1}(c) > 0 \quad \text{and} \quad M_i := Z_i^{-1}(C)$$

we have $\hat{\mathcal{K}}\hat{\mathcal{F}}_1\,|_K \subset K$. Indeed, by the estimate (33) and the monotonicity of $\hat{\mathcal{Z}}$, for $\hat{\mathcal{I}}_1 \in K$ and $i \in J_{2n-j_0}$ we have

$$\left(\hat{\mathcal{K}}\hat{\mathcal{F}}_1(\mathcal{I}_1)\right)_i = \sum_{j\in J_{2n-j_0}} \hat{k}_{ij} a_j Z_j(I_j) \ge \sum_{j\in J_{2n-j_0}} \hat{k}_{ij} a_j Z_j(m_j) = s_i\, c \ge Z_i^{-1}(c) = m_i.$$

On the other hand, by (27) and (32) we have

$$\left(\hat{\mathcal{K}}\hat{\mathcal{F}}_1(\mathcal{I}_1)\right)_i \le \sum_{j\in J_{2n-j_0}} \hat{k}_{ij} a_j Z_j(M_j) = s_i\, C \le Z_i^{-1}(C) = M_i.$$

By *Schauder fixed point theorem* there exits a fixed point for a mapping $\hat{\mathcal{K}}\hat{\mathcal{F}}_1\Big|_K$ and its uniqueness follows straight from Thm. 1 in Ciurte et al.[10]. Nevertheless, we cannot guarantee the uniqueness of fixed point in $(0,1]^{2n}$ and hence we conclude that system (11) has at least one τ-periodic solution.

In the case $\bar{J}_{2n-j_0} = \emptyset$, all the steps are analogous for s_i defined in (26), which ends the proof. □

Let us discuss a few observations related to the assumptions of Theorem 2. Using the property that operator norm $\|A\|_\infty = \max_i \sum_j |a_{ij}|$ (see Bátkai et al.[7]), we have

$$\left\|\hat{\mathcal{K}}_{22}\hat{\mathcal{A}}_2\right\|_\infty = \max_{i\in \bar{J}_{2n-j_0}} \left(\sum_{j\in \bar{J}_{2n-j_0}} k_{ij} e^{-\gamma_j \tau} \right) < 1, \tag{34}$$

guaranteeing convergence of the Neumann series and thus invariables of $(\mathrm{Id} - \hat{\mathcal{K}}_{22}\hat{\mathcal{A}}_2)$.

For diagonal matrix $\hat{\mathcal{K}}_{22}$, e.g. when we do not allow the exchange patients between

communities where bacteriae transmission is negligible[34, 32], condition (34) becomes trivial

$$\left\|\hat{\mathcal{K}}_{22}\hat{\mathcal{A}}_2\right\|_\infty = \max_{i\in\bar{J}_{2n-j_0}} k_{ii}e^{-\gamma_i\tau} < 1.$$

Nevertheless, for non-diagonal matrix $\hat{\mathcal{K}}_{22}$, e.g. when we allow the exchange patients between communities, condition (34) restricts the grow of number of colonized patients ensuring that in such units recovery rates are sufficiently large.

Now let us focus on the condition $\mathcal{R} > 1$. In the case $\beta_i > 0$ for $i \in J_{2n}$ condition $\mathcal{R} > 1$ is significantly stronger than $\mathcal{R}_0 > 1$. Indeed,

$$1 < \mathcal{R}_0 = r(\mathcal{K}\mathcal{A}) \leq \|\mathcal{K}\mathcal{A}\| = \max_{i\in J_{2n}} \sum_{j\in J_{2n}} k_{ij}a_j,$$

while

$$\mathcal{R} = \min_{i\in J_{2n}} \sum_{j\in J_{2n}} k_{ij}a_j > 1.$$

On the other hand, if we assume that transmission of the pathogen can only take place in hospitals[32, 34], then $j_0 = n$ and s_i simplifies to

$$s_i = \sum_{j\in J_n} k_{ij}a_j + \sum_{j\in\bar{J}_n} \frac{a_{j-n}k_{j,j-n}}{1-a_jk_{jj}}k_{ij}a_j.$$

4.2 Dynamics of healthcare facility network

Proposition 3 indicates that $\mathcal{R}_0$ has a strong impact on the model dynamics. Unfortunately, the formula given by (21) is not very informative in the context of spread of infection within the network and therefore we propose a sufficient condition for local asymptotic stability that clarifies the restrictions.

Using intuition form a standard SIS model, the spread of infection should depend strictly on the healthcare facilities where the transmission rate exceeds the recovery rate. In the following result we show that it is possible to obtain a stability of disease free steady state even if there exist a group of nodes v_i such that $\beta_i > \gamma_i$. This is due to the fact that patients from this group of nodes are recovering in nodes where $\beta_i < \gamma_i$. The model has this property due to a proper internal network structure, therefore we call described process the *effect of network suppression of infection.*

Let us divide all the nodes with respect to the patient average length of stay, which is given

by $\frac{1}{1-k_{ii}}$ (for details see Piotrowska et al.[32]), namely

$$J_\xi^+ := \left\{ i \in J_{2n} : \frac{1}{1-k_{ii}} > \frac{\xi+1}{\xi} \right\} \tag{35a}$$

$$J_\xi^0 := \left\{ i \in J_{2n} : \frac{1}{1-k_{ii}} = \frac{\xi+1}{\xi} \right\}, \tag{35b}$$

$$J_\xi^- := \left\{ i \in J_{2n} : \frac{1}{1-k_{ii}} < \frac{\xi+1}{\xi} \right\}, \tag{35c}$$

where ξ is an arbitrary number from $[1, \infty)$. Note that condition $k_{ii} \neq 1$ holds since otherwise it contradicts with strong connectedness of the network. The choice of conditions in (35) explains the proof of Proposition 4.

Lemma 4. *Let $\mathcal{K}$ be primitive and irreducible matrix and $\xi \in [1, \infty)$ be an arbitrary parameter. If*

$$(i) \text{ for all } i \in J_\xi^+ \qquad a_i < \frac{1 - tr(\mathcal{A})(1-k_{ii})}{k_{ii}(\xi+1) - 1}, \tag{36a}$$

$$(ii) \text{ for all } i \in J_\xi^0 \qquad tr(\mathcal{A}) < \frac{\xi+1}{\xi}, \tag{36b}$$

$$(iii) \text{ for all } i \in J_\xi^- \qquad a_i > \frac{1 - tr(\mathcal{A})(1-k_{ii})}{k_{ii}(\xi+1) - 1}, \tag{36c}$$

then disease free steady state is locally asymptotically stable.

Proof. We show that under above assumptions $r(\mathcal{K}\mathcal{A}) < 1$. Note that for matrix $\bar{\mathcal{A}} = (\bar{a}_{ij})_{i,j \in J_{2n}}$ such that

$$\bar{a}_{ij} = a_j, \quad \text{for } i, j \in J_{2n}$$

we have $\mathcal{K}\mathcal{A} = \mathcal{K} \circ \bar{\mathcal{A}}$, where $\circ$ is again a Hadamard product. By Cor. 2.1 in Zhao and Liu[50], we obtain the estimate

$$r(\mathcal{K} \circ \bar{\mathcal{A}}) \leq \max_{i \in J_\xi^+} C_i, \quad \text{with} \quad C_i := k_{ii}a_i + (r(\mathcal{K}) - k_{ii})(r(\bar{\mathcal{A}}) - a_i).$$

Obviously $r(\bar{\mathcal{A}}) = \sum_{i \in J_{2n}} a_i = tr(\mathcal{A})$ and $r(\mathcal{K}) = 1$, thus

$$C_i = k_{ii}a_i + (1-k_{ii})(tr(\mathcal{A}) - a_i) \leq a_i \left(k_{ii}(\xi+1) - 1\right) + tr(\mathcal{A})(1-k_{ii}), \tag{37}$$

for $\xi \in [1, \infty)$. Let us consider the case $k_{ii} > \frac{1}{\xi+1}$, which indicates that we focus on $i \in J_\xi^+$. The upper bound on a_i in condition (36a) is, by inequality (37), equivalent with $C_i < 1$. We note also that in order to have nonempty set of constants satisfying (36a) we need $tr(\mathcal{A})(1-k_{ii}) < 1$.

Analogous estimates in two other cases allow to show that for any $i \in J_{2n}$, that satisfies (36), $C_i < 1$ which ends the proof. □

Although conditions in Proposition 4 seem to be complex, they agree with an intuition. Let

us remind that, for $\beta_i = 0$ parameter a_i can be interpreted as a rate describing the *unsuccessful recovery process* in C- or H-node within time period τ. On the other hand, susceptible patients can also get colonized, so taking into account that fact we call $a_i = e^{(\beta_i - \gamma_i)\tau}$ the *infectiousness* of i-th node. One of the crucial parameters in this considerations is $tr(\mathcal{A})$ which is a sum of all a_i and hence we refer to it as a *network infectiousness parameter* and it allows for suppression of infection by the network itself. Note that the bound on a_i in (36) transforms into

$$\frac{1 - tr(\mathcal{A})(1 - k_{ii})}{k_{ii}(\xi + 1) - 1} = \left(\frac{tr(\mathcal{A})}{\frac{1}{1-k_{ii}}} - 1 \right) \frac{1}{1 - k_{ii}(\xi + 1)}.$$

Thus to ensure the local stability of disease-free steady state, the infectiousness a_i of each node in $i \in J_\xi^+$ needs to be balanced by the product of surplus of network infectiousness over length of stay of patients in particular node, namely $\frac{1}{1-k_{ii}}$, multiplied by the altered length of stay in the considered node if the probability of the stay in the unit would increase $(\xi + 1)$ times (keeping in mind that $k_{ii}(\xi + 1) < 1$ due to the fact that we consider $i \in J_\xi^+$). Clearly, parameter ξ was introduced to allow some flexibility in allocation of healthcare facilities in sets with lower and upper bound on infectiousness.

For simplicity consider $\xi = 1$. First, assume that the average time of a stay in some node i is longer than two days and that $tr(\mathcal{A}) > 2$. The longer patients stay in considered node, the weaker is the ability of a network to suppress an infection in this node.

Now for nodes where the average length of stay is one day, lower bound in (36c) is counterintuitive as it seems to promote higher number of infections. However, for $\mathrm{tr}(\mathcal{A}) < 1$ this condition is always satisfied. On the other hand, for fixed network and fixed $\mathrm{tr}(\mathcal{A})$, condition (36c) allows to balance the distribution of high-prevalence node within the whole network. Example 1 (iii)-(iv) shows that having two systems with the same node infectiousness' suppression effect may either hold or not. In every variant of this example, there are two nodes, with one with greater than one and second with smaller than one infectiousness, connected in both directions. Intuitively, the node with greater than one infectiousness shall develop non-zero endemic state and spread it to the other node. However, we show cases where this behaviour is suppressed by sufficient transfer rates from smaller than one infectiousness node.

Example 1. *Consider system* (11) *with* $\tau = 1$ *and four sets of parameters. Case (i) (resp. (ii)) shows that conditions* (36) *can be satisfied for* $a_i > 1$ *and* $i \in J_\xi^+$ *(resp.* $i \in J_\xi^-$*), while the next two indicates that lower bound in* (36c) *allows for appropriate location of high-prevalence nodes in the network structure. In all cases the network structure in the system is given by a column stochastic, primitive and irreducible matrix* $\mathcal{K} \in M_{2\times 2}([0,1])$ *and the node transmission and recovery rates by* $\mathbf{B} = diag(\beta_i)_{i=1,2}$ *and* $\Gamma = diag(\gamma_i)_{i=1,2}$.

(i) $\mathcal{K} = \begin{bmatrix} 0.7 & 0.6 \\ 0.3 & 0.4 \end{bmatrix}$, $\beta_1 - \gamma_1 = \ln 1.1$, $\beta_2 - \gamma_2 = \ln 0.1$

According to formulas (13) – (15) *we have* $\mathcal{A} = diag\,(1.1, 0.1)$. *Conditions in Proposition 4*

are satisfied since $\sigma(\mathcal{K}) = \left\{\frac{1}{10}, 1\right\}$, $J_1^+ = \{1\}, J_1^- = \{2\}$, $tr(\mathcal{A}) = 1.2$

$$\begin{aligned} a_1 = 1.1 &< 1.6 = \frac{1 - tr(\mathcal{A})(1 - k_{11})}{2k_{11} - 1}, \\ a_2 = 0.1 &> -1.4 = \frac{1 - tr(\mathcal{A})(1 - k_{22})}{2k_{22} - 1}. \end{aligned}$$

Furthermore $r(\mathcal{KA}) = \frac{\sqrt{1621}+81}{200} < 1$.

(ii) $\mathcal{K} = \begin{bmatrix} \frac{3}{4} & \frac{2}{3} \\ \frac{1}{4} & \frac{1}{3} \end{bmatrix}$, $\beta_1 - \gamma_1 = \ln 0.5$, $\beta_2 - \gamma_2 = \ln 1.5$

According to formulas (13) – (15) *we have* $\mathcal{A} = diag\left(\frac{1}{2}, \frac{3}{2}\right)$. *Again the conditions in Proposition 4 hold since* $\sigma(\mathcal{K}) = \left\{\frac{1}{12}, 1\right\}$, $J_1^+ = \{1\}, J_1^- = \{2\}$, $tr(\mathcal{A}) = 2$ *and*

$$\begin{aligned} a_1 = \frac{1}{2} &< 1 = \frac{1 - tr(\mathcal{A})(1 - k_{11})}{2k_{11} - 1}, \\ a_2 = \frac{3}{2} &> 1 = \frac{1 - tr(\mathcal{A})(1 - k_{22})}{2k_{22} - 1}, \end{aligned}$$

Moreover $r(\mathcal{KA}) = \frac{\sqrt{33}+7}{16} < 1$.

(iii) $\mathcal{K} = \begin{bmatrix} 0.1 & 0.51 \\ 0.9 & 0.49 \end{bmatrix}$, $\beta_1 - \gamma_1 = \ln 0.89$, $\beta_2 - \gamma_2 = \ln 1.1$

Repeating the calculations we have $\mathcal{A} = diag(0.89, 1.1)$, $\sigma(\mathcal{K}) = \{-0.41, 1\}$, $J_1^- = \{1, 2\}$ *and* $tr(\mathcal{A}) = 1.99$. *This time however condition* (36c) *does not hold since*

$$a_1 = 0.89 < 0.98875 = \frac{1 - tr(\mathcal{A})(1 - k_{11})}{2k_{11} - 1}.$$

The disease free steady state is not asymptotically stable because $r(\mathcal{KA}) > 1.021$.

(iv) $\mathcal{K} = \begin{bmatrix} 0.1 & 0.51 \\ 0.9 & 0.49 \end{bmatrix}$, $\beta_1 - \gamma_1 = \ln 1.1$, $\beta_2 - \gamma_2 = \ln 0.89$

In this case the only difference, comparing to (iii) is the swap of infectiousness parameters between healthcare facilities 1 and 2. We have $\mathcal{A} = diag(1.1, 0.89)$, $\sigma(\mathcal{K}) = \{-0.41, 1\}$, $J_1^- = \{1, 2\}$ *and* $tr(\mathcal{A}) = 1.99$, *however, now condition* (36c) *is satisfied*

$$\begin{aligned} a_1 = 1.1 &> 0.98875 = \frac{1 - tr(\mathcal{A})(1 - k_{11})}{2k_{11} - 1}, \\ a_2 = 0.89 &> 0.745 = \frac{1 - tr(\mathcal{A})(1 - k_{22})}{2k_2 - 1}. \end{aligned}$$

The disease free steady state is asymptotically stable, $r(\mathcal{KA}) < 0.963$.

Lemma 5. *Under the assumptions of Proposition 4, the network suppression effect is possible only if there is no more then one $i \in J_\xi^+$ such that $a_i \geq 1$.*

Proof. Note that for $\mathrm{tr}(\mathcal{A}) > 2$ there are no parameters of the model such that for $i \in J_\xi^+$ conditions

$$\frac{1 - tr(\mathcal{A})(1 - k_{ii})}{k_{ii}(\xi + 1) - 1} > 1, \tag{38}$$

are satisfied. Clearly, $i \in J_\xi^+$ implies that

$$1 - k_{ii}(\xi + 1) < 0. \tag{39}$$

To show this, let us consider two cases.

First, let $\mathrm{tr}(\mathcal{A}) > \xi + 1$, then $k_{ii} \in \left(\frac{2-\mathrm{tr}(\mathcal{A})}{\xi+1-\mathrm{tr}(\mathcal{A})}, 1\right]$ which is an empty set for $\xi \geq 1$.

Now let $\mathrm{tr}(\mathcal{A}) \leq \xi + 1$. Since (39), thus to have (38) inequality $tr(\mathcal{A})(1 - k_{ii}) < 1$ needs to hold. Consequently we obtain the bound on k_{ii},

$$k_{ii} \in \left(\frac{tr(\mathcal{A}) - 1}{tr(\mathcal{A})}, \frac{2 - tr(\mathcal{A})}{\xi + 1 - tr(\mathcal{A})}\right),$$

and the above set is nonempty only for $tr\mathcal{A} < \frac{\xi+1}{\xi}$. In addition $\frac{\xi+1}{\xi} \leq 2$ holds. We conclude that if there is more than one healthcare facilities in J_ξ^+ with $a_i > 1$, then $tr(\mathcal{A}) > 2$ and conditions (36) does not hold. □

Proposition 5 indicates that Proposition 4 can be used in the networks where all but one of the nodes belong to J_ξ^- set. However when more then one node is in J_ξ^+ set, it is better to consider another sufficient condition guaranteeing the local stability of disease-free steady state given in the following proposition. One of the main advantages of proposed approach is not only to give a new result that can be easily checked but also to gather a few intuitive observations. Furthermore, it indicates that restriction noticed in Proposition 5 is not of general nature.

Lemma 6. *Let $\mathcal{K}$ be primitive and irreducible matrix. If there exits a parameter $\alpha \in [0, 1]$ such that for all $i \in J_{2n}$*

$$\left(\sum_{j \in J_{2n}} k_{ij} a_j\right)^{\alpha} a_i^{1-\alpha} < 1, \tag{40}$$

then disease-free steady state is locally asymptotically stable.

Proof. The result is based on the bound for the maximal characteristic root of nonnegative

irreducible matrix derived by Ostrowski et al.[29, 30]. Namely,

$$\begin{aligned} r(\mathcal{K}\mathcal{A}) &= \max_{i\in J_{2n}} \left(\sum_{j\in J_{2n}} k_{ij}a_j\right)^{\alpha} \left(\sum_{s\in J_{2n}} k_{si}a_i\right)^{1-\alpha} \\ &= \max_{j\in J_{2n}} \left(\sum_{j\in J_{2n}} k_{ij}a_j\right)^{\alpha} \left(\sum_{s\in J_{2n}} k_{si}\right)^{1-\alpha} a_i^{1-\alpha}. \end{aligned}$$

By columns stochasticity of $\mathcal{K}$ and Proposition 3 we have a thesis. □

Note that choosing $\alpha = 0$ we obtain standard stability condition for SIS model, namely that all recovery rates exceed transmission rates $\gamma_i > \beta_i$.

Condition (40) for $\alpha = 1$, namely $\sum_j k_{ij}a_j < 1$, limits the number of infectious patient in i-th place, directly caused by one patient entering it from any other place. From analytical perspective we recognise this condition as one of the conclusions from *Perron theorem*, see for instance Meyer[25] para. 8.2.7.

For $\alpha = \frac{1}{2}$ condition (40) reads

$$\sum_{j\in J_{2n}} k_{ij}a_j < \frac{1}{a_i} \quad \Longleftrightarrow \quad \sum_{j\neq i} k_{ij}a_j < \frac{1}{a_i} - k_{ii}a_i \quad \text{for all } i \in J_{2n}. \tag{41}$$

Expression $k_{ij}a_j = k_{ij}e^{(\beta_j-\gamma_j)\tau}$ can be interpreted as a probability that patients from node j that remained colonized or get colonized after time τ spent in node j was moved to i-th node. Thus, $\sum_{j\neq i} k_{ij}a_j$ would correspond to the inflow to node i still infectious patients from all other nodes and if it is properly restricted then the stability of disease free steady state is guarantied. Hence, condition (41) allows us to select nodes to which countermeasures preventing the spread of the pathogen within the network should be addressed.

It allows to derive the following example.

Example 2. *Consider system* (11) *with* $\tau = 1$ *and the following set of parameters*

$$\mathcal{K} = \begin{bmatrix} 0.51 & 0 & 0.1 & 0.1 \\ 0.2 & 0.51 & 0 & 0.1 \\ 0.29 & 0 & 0.8 & 0 \\ 0 & 0.49 & 0.1 & 0.8 \end{bmatrix}, \qquad \mathbf{B} - \Gamma = diag\,(\ln 1.3, \ln 1.1, -\ln 2, -\ln 2)$$

According to formulas (13) – (15) *we have* $\mathcal{A} = diag\,(1.3, 1.1, 0.5, 0.5)$, *and since* $\#\{\lambda : |\lambda| = r(\mathcal{K}\mathcal{A})\} = 1$, $\mathcal{K}$ *irreducible. We note now that* $tr(\mathcal{A}) = 3.4$ *and* $J_\xi^+ = J_4$ *for any* $\xi \geq 1$. *The assumptions of Proposition 6 are satisfied for* $\alpha = \frac{1}{2}$ *and indeed* $r(\mathcal{K}\mathcal{A}) < 0.82$.

5 Numerical simulations in relation to previous study

The theoretical considerations presented above not only validate previous numerical simulations but also improve our understanding of the network components on the dynamics of the SIS-type pathogen (e.g. multidrug-resistant bacteriae) transmission in the healthcare system. In particular, local stability results agree with global numerical observations about two possible behaviours of the system. Either the disease-free steady state is asymptotically stable, and then the disease "will die out" within infinite time horizon, or it is unstable, so then even one colonized patient introduced to the system will lead to the propagation of the pathogen within the system and its persistent presence e.g. due to the existence of locally asymptotically stable endemic steady state or τ-periodic solutions. Unfortunately, the spread of hospital-acquired infections in the European population leads to a bitter conclusion that in real systems we deal with the latter. Then, the general question arises: is it possible to modify the existing system, limiting the necessary cost as much as possible, such that the asymptotically stable state will be the disease-free state? On the other hand, if the disease-free state is not an option, how to at least lower the prevalence of bacteria in the network?

The obvious intervention would be decreasing the transmission probability globally, i.e. by global increase of the hygienic standards, limit antibiotics usage, isolate colonized patients or high-risk patients etc. in all hospitals. This would lead to global decrease of transmission levels β_i, and as $\max_i \beta_i \to 0$ this would eventually lead to stability of disease-free steady state. However, assuming that this is feasible at all, the economic burden on society would be enormous. Thus, the natural approach is to limit the interventions only to some part of the system, i.e. to focus the interventions in precisely chosen units, not only lowering the prevalence there, but also decreasing it globally.

The first step towards this goal is to determine which healthcare units are most prone to the high prevalence of bacteriae. By the prevalence in the i-th node $\mathrm{Prev}_i(t)$ and a system-wide prevalence $\mathrm{Prev}(t)$, at time $t \geq 0$, we understand

$$\mathrm{Prev}_i(t) = \frac{I_i(t)}{H_i(t)}, \qquad \mathrm{Prev}(t) = \frac{\sum_{i \in J_{2n}} I_i(t)}{\sum_{i \in J_{2n}} H_i(t)},$$

respectively. In order to make sure that above parameters stabilise at certain level, in computer simulations we consider only $t = k\tau$, $k \in \mathbb{N} \cup \{0\}$. It is demonstrated by numerical simulations that high prevalence in healthcare facilities is correlated to their average length of stay[34]. Also, the basic reproduction number estimated for a one hospital-community pair (*HC-pair*), can be used for this purpose[32]. It is worth to underline that listed results take into account only local properties of a given unit and do not exploit the healthcare network properties directly.

Results of this study lead to indicators of units for interventions, which also take into account the network structure. We determine network basic reproduction number $\mathcal{R}_0$, defined in (21), indicating that stable disease-free state is locally asymptotically stable for $\mathcal{R}_0 < 1$. It cannot be

used directly to point to specific units, but it may be used to evaluate if the proposed intervention is promising. Then, there is a parameter s_i defined in (27), which takes into account the pathogen spread in a given node and the network structure. In the following we focus on another parameter

$$r_i := \sum_{j \in J_{2n}} k_{ij} a_j - \frac{1}{a_i}, \tag{42}$$

which arises due to subtracting right-hand side from left-hand side of (41). In particular, if $r_i < 0$ for all nodes, then the disease-free steady state is locally asymptotically stable due to Proposition 6 with $\alpha = 1/2$.

To investigate the potential of our analytical findings we use a computational network based model of healthcare system of Lower Saxony (Germany). The model is based on anonymized insurance data provided by AOK Lower Saxony — a healthcare provider in Germany, for more information on these data we refer interested reader to our technical report[33]. Previously proposed computational model[34], that is also used in this simulations, corresponds to the theoretical model presented in Section 2 with $\tau = 1$ day. It describes dynamics of 164 hospital nodes (*H-nodes*) and the same amount of corresponding community nodes (*C-nodes*). As an initial state, 1% of colonized population uniformly distributed among total population is assumed and all simulations are conducted for a period of 7 000 days. More details on the numerical model may be found in Piotrowska et al.[34] while the code and documentation of the package can be downloaded[1].

The previous study[34, 32] focused on hospital inquiry infections thus also now we assume no multidrug-resistant bacteriae transmission in C-nodes. Moreover, we assume that transmission characteristics in all hospitals are the same ($\beta_i = \beta$) and that spontaneous recovery is the same in all nodes. The choice $\gamma_i = 1/365$ day^{-1} and $\beta_i = 0.065$ day^{-1} (for H-nodes) for the network (built based on data provided by AOK Lower Saxony and for the patient-transfer matrix[34]) resulted in stabilization (within a period of 7 000 days) of the system-wide community prevalence (understood as a fraction of all colonized patients staying in C-nodes) and the system-wide hospital prevalence (understood as a fraction of all colonized patients staying in H-nodes) at the level of 8.87% and 21.98%, respectively. These results are close to values reported in the literature for ESBL-producing Enterobacteriaceae (*Escherichia coli* and *Klebsiella pneumoniae*)[37], third-generation cephalosporin-resistant *Escherichia coli*[17] and third-generation cephalosporin-resistant *Enterobacteriaceae* in general[38].

The time evolution of the prevalence within the simulated period is presented in Figure 1. The prevalence at the end of simulation do not change much, thus we assume that we are sufficiently close to the stable state or τ-periodic solution at the last simulated day. Since most likely it is not the stable state itself, later on we will call it *final state*.

The interesting observation, that clearly indicates the importance of system approach, is the large difference in prevalence between particular facilities (in final states), although they do

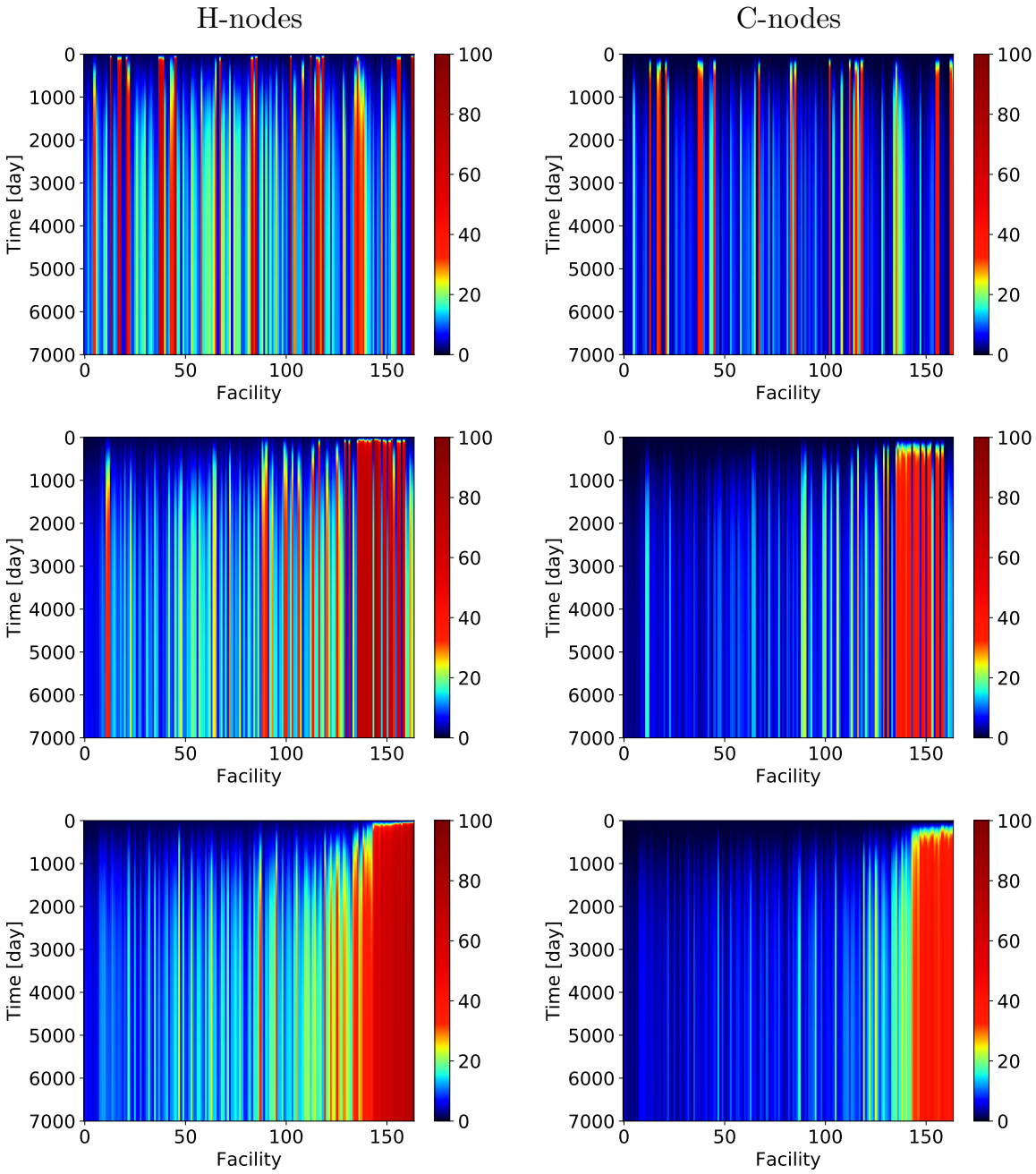

Figure 1: Change of the prevalence in healthcare facilities (left) and corresponding community nodes (right) in time. In first row, sort order was based on facility index in the patient-transfer matrix, which is not related to any particular parameter of the facility. In second row, nodes are ordered by increasing s_i parameters (see (27)) of H-nodes (C-nodes are also sorted by corresponding H-node parameters). In second row, nodes are ordered by increasing r_i parameters (see (42)) of H-nodes (C-nodes are also sorted by corresponding H-node parameters). Separate sort order for C-nodes is not introduced to show the correspondence between H-node prevalence and C-node prevalence. Prevalence is shown at transfer moments (once per day), so we do not observe daily fluctuations in these figures.

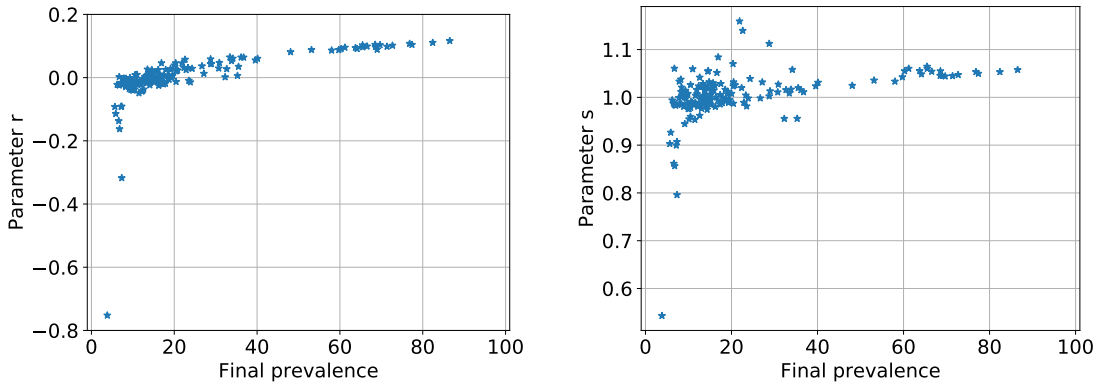

Figure 2: H-node parameter r_i (left) and s_i (right) versus final prevalence in corresponding H-nodes.

not have different properties regarding the transmission and recovery parameters. If facilities are sorted by s_i parameter (with the same sort order for C-nodes, i.e. by their corresponding H-node s_i parameter), we note that some order is imposed on their prevalence. Namely, H-nodes and C-nodes with high prevalence are more likely to occur for higher values of s_i (see Figure 1 middle row). If we take r_i instead, the correspondence is even better, as shown in Figure 1 bottom row.

While the dependence of the final prevalence on the r_i parameter is not monotone (see also Figure 2), we clearly see that high prevalence are reached for facilities with high r_i, while this is not exactly the case for s_i. This observation is promising, as we expect the high-prevalence facilities to be an important source of colonized patients in the healthcare network and r_i parameters seem to better grasp some of the properties of nodes in the healthcare system network. Moreover, Proposition 6 suggest a natural goal to achieve: reduce $r_i \geq 0$ parameters for H-nodes accordingly. Reduction will be performed by decreasing β_i by half, which we interpret as local (hospital-level) countermeasures. Here we do not want to go deeper into the nature of these interventions, but rather to verify if this approach has a chance of success and to check how much we would be able to reduce the system-level prevalence.

The procedure is then as follows. We start with the original network, with $\beta_i = 0.065$ day^{-1} for H-nodes ($\beta_i = 0$ in C-nodes) and $\gamma_i = \frac{1}{365}$ day^{-1} for every node. We pick a H-node with maximal r_i parameter and reduce in this node β_i by a factor of two, and we run the simulation to check the system-wide (hospital and community) prevalence. Note that by reducing a given β_i, all r_j values may change — not only r_i since the whole network is affected by this change. Although, since a_i dependents on β_i, and k_{ii} is likely to be the maximal value of i-th row of the matrix $\mathcal{K}$ (probability of remaining in any node is likely to be larger than probability of transfer/admission/discharge), then we expect that change of β_i will have the most significant impact on r_i. Next, we pick a H-node with maximal r_i again and repeat the procedure until the satisfactory prevalence reduction will be obtained. Note that repeated reductions in the same facility are possible.

Impact of successive transmission rates reductions on final system-wide hospital and

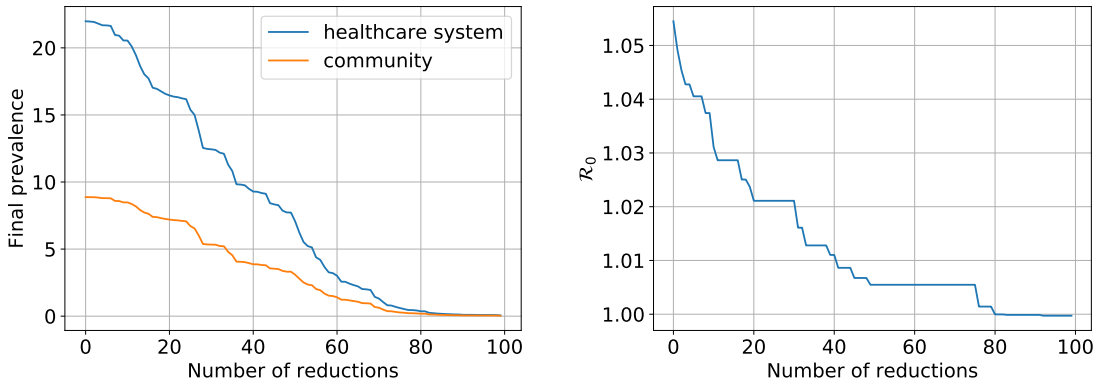

Figure 3: System-wide (hospital and community) prevalence and $\mathcal{R}_0$ parameter versus number of transmission rates reductions.

community prevalence in the healthcare system and $\mathcal{R}_0$ parameter are shown in Figure 3. Before transmission rates reductions, 21.98% system-wide hospital prevalence and 8.87% system-wide community prevalence was observed (cf. Figures 4 and 5). We see that initially, the both prevalences decreases slowly. After 16 reductions, system-wide hospital prevalence decreased to about 17% (7.5% in community, while after 48 reductions, system-wide hospital prevalence decreased below 8% (over 3% in community). To lower the system-wide hospital prevalence below 3%, 61 reductions are necessary. For 72 and more reductions, it is less than 1%. At 80-th reduction, $\mathcal{R}_0$ drops below 1. At that point, we expect the disease-free state to be stable. While in simulations we still observe a non-zero prevalence (0.4% in system-wide hospital, 0.2% system-wide community), exactly zero may be impossible to observe in finite-time simulations. The last simulation, with 99 reductions, resulted in system-wide hospital prevalence below 0.06%.

At the beginning, the described procedure reduces transmission rates in different facilities successively (see Figure 6). However, for further iterations we observe repeated reductions in the same facilities. The highest number of transmission rates' reductions in the same facility that we observe is 3. Nevertheless, it is present only in few facilities. To obtain $\mathcal{R}_0 < 1$ (80 reductions), only two triple reductions are necessary, and only 57 facilities out of 164 in total are covered by additional preventive countermeasures — other facilities need not to be affected. Additionally, in Figure 7 we present the change of r_i values after selected iterations confirming correctness of proposed procedure.

6 Conclusions

Both analytical and numerical results presented in the above considerations are crucial to understand the network structural influence on the dynamics of infection spread. The effect of network suppression proved in Prepositions 4 and 6, indicates that simple intuitions based on decoupled systems may fail. Even having parameters $\beta_i > \gamma_i$, for some units $i \in J_{2n}$ we can still expect asymptotic damping of infection. It is further confirmed in calculations of parameter

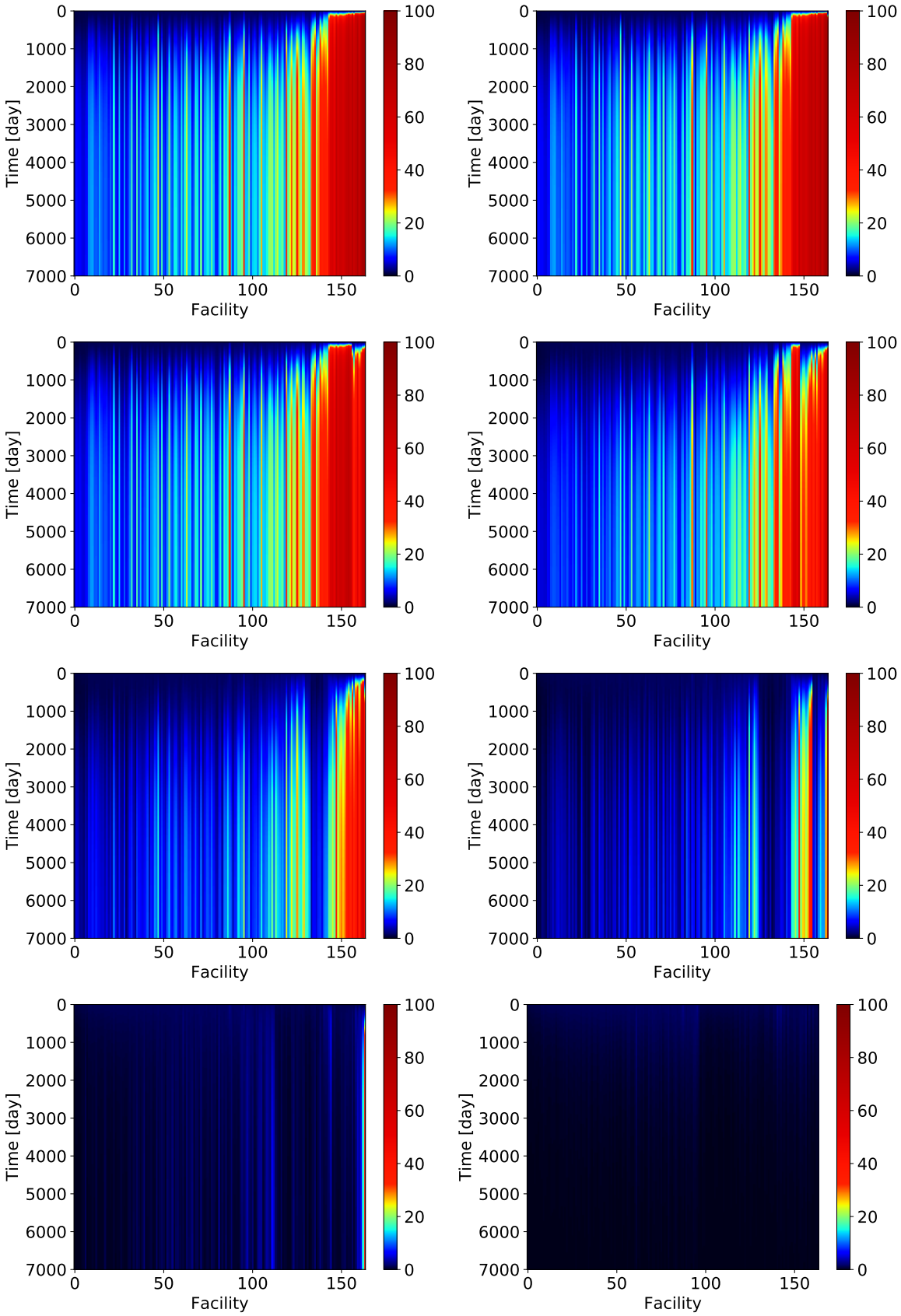

Figure 4: Change of the prevalence in healthcare facilities (H-nodes) in time for different number of transmission reductions: 0 (original system), 1, 8, 16, 32, 48, 70, 95. All figures are sorted by increasing H-node r_i values for original system.

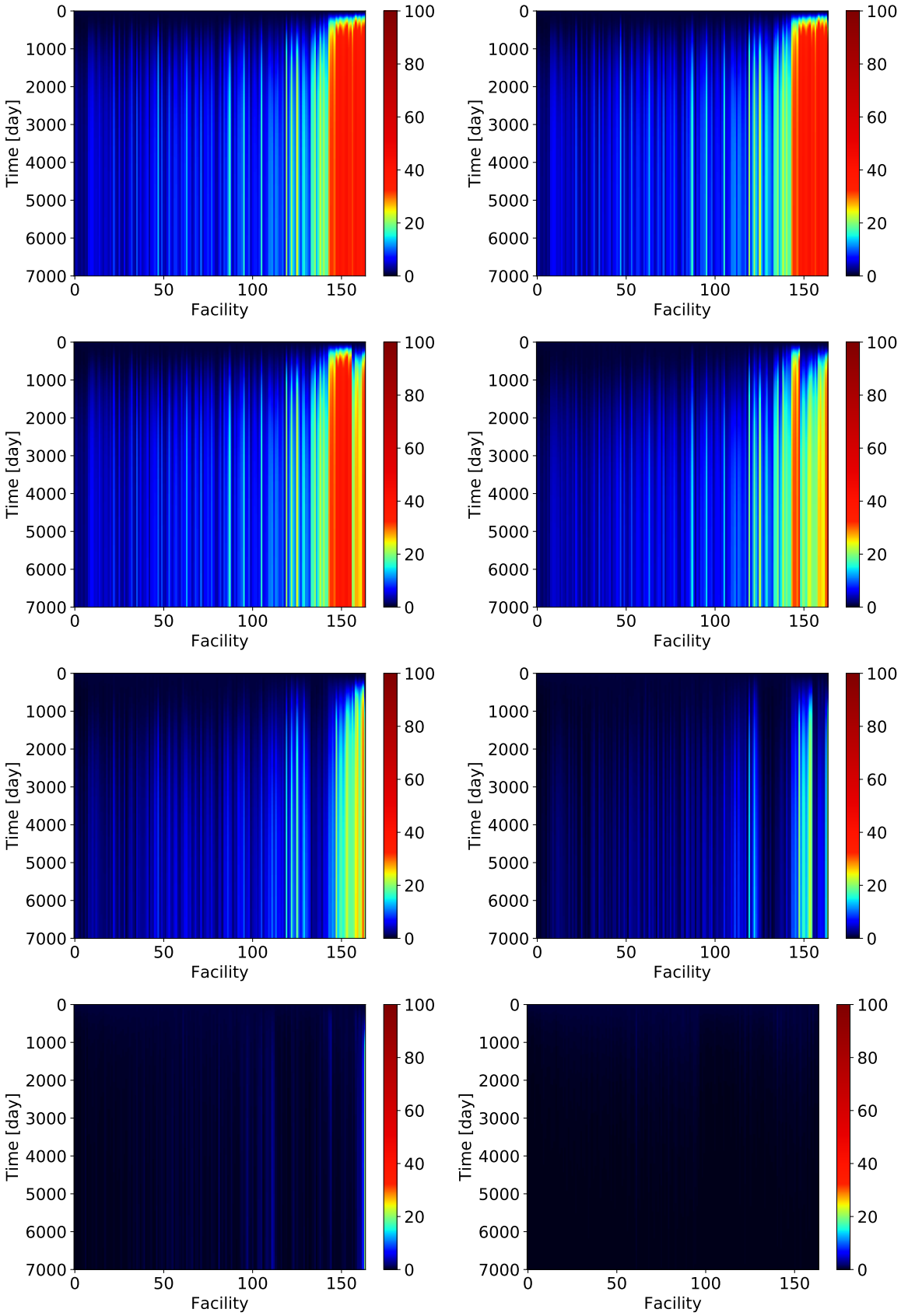

Figure 5: Change of the prevalence in community (C-nodes) in time for different number of transmission reductions: 0 (original system), 1, 8, 16, 32, 48, 70, 95. All figures are sorted by increasing H-node r_i values for original system.

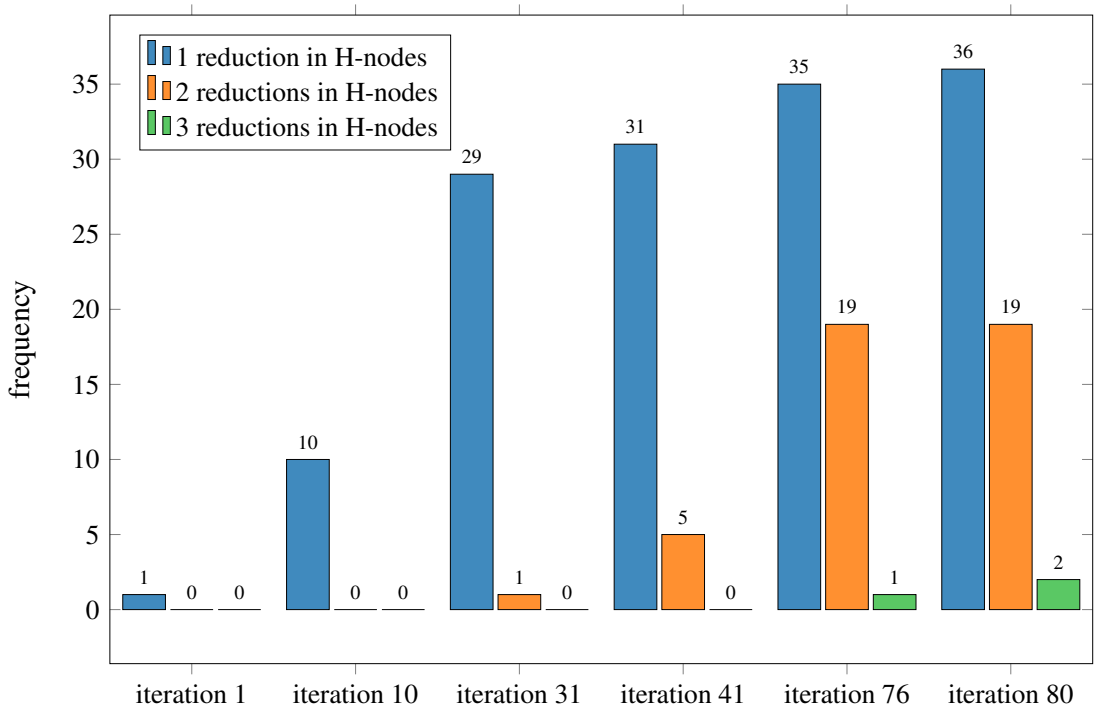

Figure 6: Transmission reduction factor in healthcare facilities for different number reduction algorithm iterations: 1, 10, 31, 41, 76 and 80. After 80 iterations system R_0 given by (21) is smaller then 1.

r_i presented in Section 5, which can differ substantially although transmission and recovery parameters are the same in all hospitals. In view of the above, the mechanism of sorting the healthcare facilities in order to determine which of them are more prone to the high system prevalence clearly indicates good places in the network to control the infection.

Numerical simulations justify two sorting methodologies. The first establishes the order in the set of units with respect to the value of parameter r_i; and its effectiveness is confirmed by Figures 4 and 5 (top rows). We can also propose another sorting which divides all units with respect to number of transmission rates' reductions in the procedure in Section 5, compare Figure 6. Reductions of β parameter should be conducted until the conditions $r_i < 0$ hold for all $i \in J_{2n}$ and thus $\mathcal{R}_0 < 1$ is satisfied guarantying local stability of decease free steady state. In particular, for computational network based model of healthcare system of Lower Saxony, after 80 algorithm iterations we divide all units into compartments due to the number of reductions that affected particular healthcare facility nodes abating four compartments C_0 up to C_3 with indexes indicating the number of reductions:

$$|C_0| = 107, \qquad |C_1| = 36, \qquad |C_2| = 19 \qquad |C_3| = 2.$$

It is natural to ask about the correlation between the final hospital/community prevalence and other standard network measures both local (such as H-nodel/C-node in-/out-degrees;

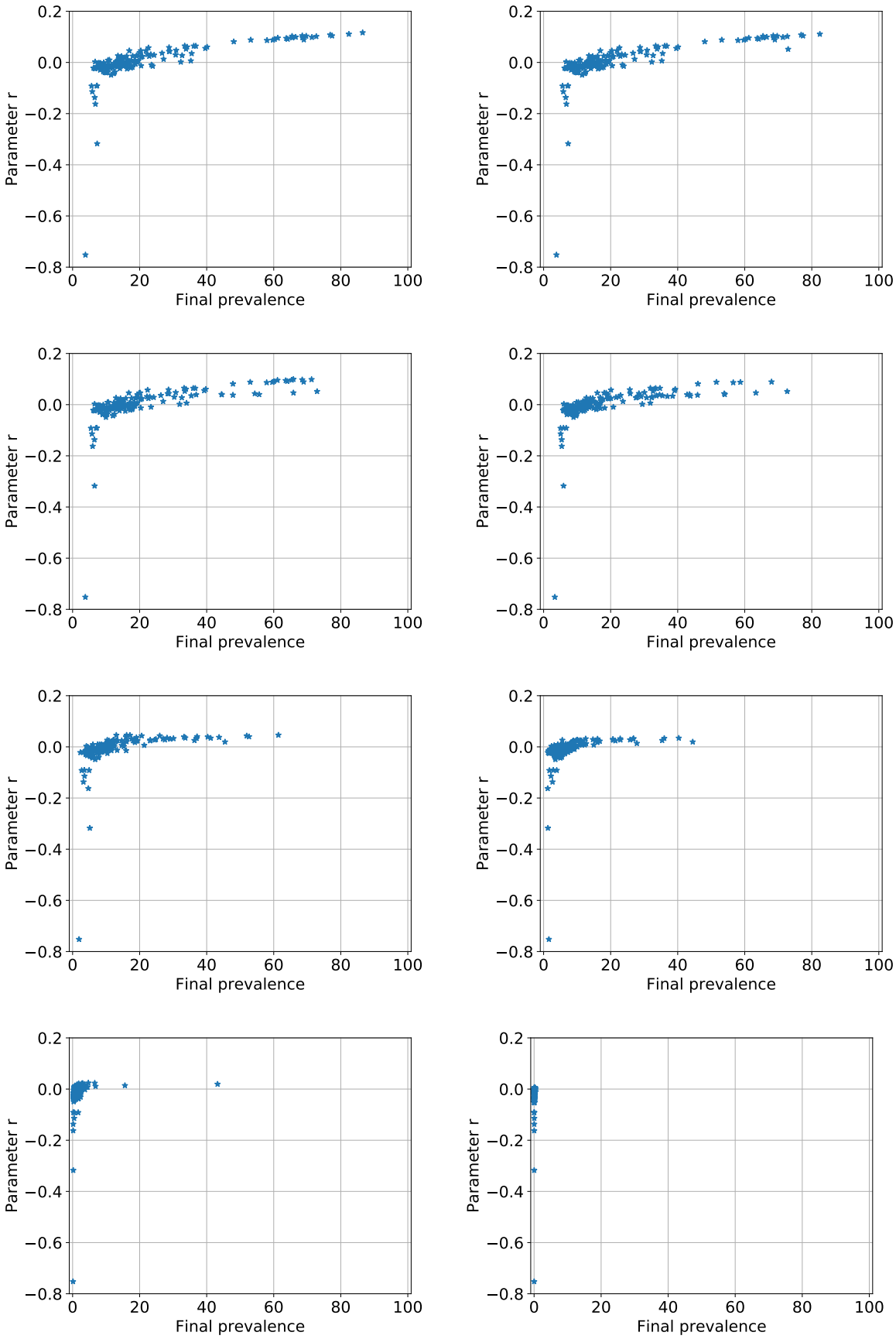

Figure 7: H-node r_i parameter versus prevalence for different number of transmission reductions: 0 (original system), 1, 8, 16, 32, 48, 70, 95. All figures are sorted by increasing H-node r_i values for original system.

average length of stay in nodes; node in-/out-strength; closeness in-/out-centrality) and global ones (graph radius, diameter and density). In the light of considerations of Piotrowska et al.[34], we do not expect here a breakthrough, however deeper analysis of the corrections between node prevalence and some more sophisticated network measures might be addressed in the future.

Another interesting direction of further considerations is the investigation on the relationship between parameter $\mathcal{R}_0$ and both the system-wide and H-node (resp. C-node) prevalence. Even having explicit formulas for functions $\mathcal{H}$ and $\mathcal{I}$, see (7) and (17), it is not clear how to establish this relation analytically. In our simulations we observe that decrease of prevalence (system-wide hospital and system-wide community) is accompanied by decrease of $\mathcal{R}_0$ (see Figure 3). The observed pattern suggests a hypothesis that a network with lower $\mathcal{R}_0$ would results in a lower prevalence. Since calculating $\mathcal{R}_0$ for a network model is much faster than performing a pathogen dynamics simulation, it would be an efficient parameter for comparison of different networks' susceptibility on a given pathogen. While it is no substitute for a full-scale simulation, it could improve initial process of developing modifications of existing healthcare system networks by efficiently indicating of more or less promising propositions.

Finally, except from indicting units where the cost of transmission reduction compared to the global effect is the lowest, we can consider little costly good practices to decrease the colonisation. Prepositions 4 and 5 clearly indicate that it is easier to obtain network suppression of infection if there are more units from a set J_ξ^-, see Definition (35c), i.e. with average length of stay equal to 1. It goes in line with previous results on decoupled systems which stated the correlation between high prevalence in healthcare facilities and the average length of stay. Translating obtained property into suggestion that can be given to police-makers responsible for hospital network management; we propose to promote system in which in well-considered cases patients are discharged from the hospital for weekends instead of being kept for two more days without serious reason. It is worth to thought through this suggestion because, except from medical reasons, it also reduces hospital costs. In order to confirm our hypothesis further considerations in this direction should be conducted, changing the model so that it takes into consideration the lack of discharge from hospitals in the weekends. Another specification that should be included is the possible growth in number of admissions on Mondays due to wrong diagnosis at the end of a previous week.

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