Epidemics 33 (2020) 100408

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

Impact of inter-hospital transfers on the prevalence of resistant pathogens in a hospital–community system

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ARTICLE INFO

Keywords:
Healthcare network
Epidemiology
Healthcare associated infections
Basic reproduction number
Multidrug resistant Enterobacteriaceae

ABSTRACT

The spread of resistant bacteria in hospitals is an increasing problem worldwide. Transfers of patients, who may be colonized with resistant bacteria, are considered to be an important driver of promoting resistance. Even though transmission rates within a hospital are often low, readmissions of patients who were colonized during an earlier hospital stay lead to repeated introductions of resistant bacteria into hospitals. We developed a mathematical model that combines a deterministic model for within-hospital spread of pathogens, discharge to the community and readmission, with a hospital–community network simulation of patient transfers between hospitals. Model parameters used to create the hospital–community network are obtained from two health insurance datasets from Germany. For parameter values representing transmission of resistant Enterobacteriaceae, we compute estimates for the single admission reproduction numbers R_A and the basic reproduction numbers R_0 per hospital–community pair. We simulate the spread of colonization through the network of hospitals, and investigate how increasing connectedness of hospitals through the network influences the prevalence in the hospital–community pairs. We find that the prevalence in hospitals is determined by their R_A and R_0 values. Increasing transfer rates between network nodes tend to lower the overall prevalence in the network by diluting the high prevalence of hospitals with high R_0 to hospitals where persistent spread is not possible. We conclude that hospitals with high reproduction numbers represent a continuous source of risk for importing resistant pathogens for hospitals with otherwise low levels of transmission. Moreover, high risk hospital–community nodes act as reservoirs of pathogens in a densely connected network.

1. Introduction

Healthcare-associated infections (HAI) are found to cause substantial burden on population health (Cassini et al., 2016), and infections with resistant pathogens are responsible for increasing morbidity and mortality in Europe (Cassini et al., 2019). In recent years, increased levels of resistance in *Enterobacteriaceae*, especially plasmid mediated resistance via ESBLs, has sparked concern and led to intensified intervention efforts. Difficulty in designing effective interventions is due to the asymptomatic nature of colonization with resistant bacteria and to the variety of transmission routes. Since it is hard to assess the relevance of a specific transmission route and to determine the efficacy of a particular intervention to limit the spread of HAI (Pham et al., 2019), mathematical modelling has been used to understand the key driving factors of HAI transmission and to assess the impact of specific interventions or bundles of various intervention strategies (Grundmann and Hellriegel, 2006; van Kleef et al., 2013).

As hospitals are not closed populations, the in- and outflow of patients from the hospitals are likely to play an important role in HAI transmission dynamics. The majority of patients who are discharged from a hospital go back to the community, and few are referred to other hospitals. Since not all patients returning to the community are decolonized, the community acts as a reservoir. Sporadic outbreaks inside hospitals may occur due to readmission of individuals colonized during preceding hospital admissions (Robotham et al., 2007). In a modelling study of the interaction between hospital and community transmission (Cooper et al., 2004), the authors showed that frequent readmissions of colonized patients into a hospital from a community reservoir can lead to sustained transmission of resistant pathogens even if within-hospital transmission alone is not sufficient for persistent

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https://doi.org/10.1016/j.epidem.2020.100408
Received 29 January 2020; Received in revised form 21 August 2020; Accepted 7 October 2020
Available online 21 October 2020

spread of the pathogen. The authors introduced the concept of the single admission reproduction number R_A, which denotes the number of secondary cases produced by a colonized patient during his entire admission period in the hospital. This number may be different from the basic reproduction number R_0, which denotes the total number of secondary cases produced by a patient during his entire period of colonization, which could comprise several hospital admissions. From these definitions it is clear that $R_0 \geq R_A$, and we can have the situation that $R_0 > 1$, while $R_A < 1$. In their paper (Cooper et al., 2004), Cooper et al. gave several estimates for R_A for *methicillin resistant Staphylococcus aureus* (MRSA) based on data, which are all below 1. Similarly, in Gurieva et al. (2017), the authors provide estimates for R_A for antibiotic resistant *Enterobacteriaceae* in intensive care units, all of which are also below 1.

Likewise, Smith et al. (2004, 2005) showed that the prevalence in a hospital may remain on a constant level owing to admissions of colonized individuals from the community, other hospitals, and long-terms care facilities. In another modelling study, Robotham et al. (2006) investigated the link between hospital and community in terms of the effect of surveillance and infection. All these studies provide evidence for the importance of patient movements between hospitals, long-term care facilities and the communities (catchment populations).

In the past decade, the role of patient movements between hospitals has been studied, and patient transfers between hospitals have been visualized as networks, e.g. in the Netherlands (Donker et al., 2010, 2012), the United Kingdom (Ciccolini et al., 2013; Donker et al., 2017), France (Nekkab et al., 2017), and the USA (Huang et al., 2010). Although patient referral network studies provide useful insights on pathogen spread between hospitals, the role of hospital catchment areas (community served by a specific hospital) in pathogen spread is not well studied. The aim of the current work is to combine a simple model of patient exchange between hospital and community with a network of patient flows between network nodes. We formulate a deterministic SIS-type model (*susceptible–infectious–susceptible*), for within-hospital spread and combine it with a process of readmission and discharge to a community, in which no transmission takes place. Based on datasets provided by two German health insurance companies, the patient movement network is then formed by a collection of hospital–community pairs (*HC-pairs*). We estimate single admission reproduction numbers R_A per hospital based on average length of stay per hospital. Then, we simulate the spread of pathogen through the network of connected hospitals, where hospital sizes and patient flows are quantified from the datasets. Our aim is to gain insight into how the prevalence in the entire system is governed by transmission dynamics in the HC-pairs. Moreover, we study how connection in a network of hospitals influences the prevalence in hospital–community pairs.

2. Basic deterministic model for unconnected hospitals

We formulate a susceptible–infectious–susceptible (SIS) model for the spread of infection within a single hospital and extend it by modelling the role of discharge to and admission from the community. The model is a simplified version of the model introduced by Cooper et al. (2004) to describe the role of readmissions on dynamics of hospital infections. It should be noted here that in this work we do not distinguish between colonization and infection, but use the terms interchangeably.

The variables of the model are defined as fractions of the population as follows: susceptible individuals in the hospital S, colonized individuals in the hospital I, susceptible individuals in the community V, and colonized individuals in the community W. We assume that pathogen transmission takes place only in the hospital, and only the susceptible individuals during their hospital stay are exposed to colonized individuals in the hospital. Parameter β is the transmission rate, and colonized individuals in hospital and in community clear their colonization at the same rate γ. Patients are discharged at rate α and readmitted at rate ϵ. Furthermore, we assume that patients are screened at admission, and if they are found positive, they are decolonized with probability $0 \leq \sigma \leq 1$. They then enter the hospital as susceptible.

Note that the community defined in our model only contain individuals who have been discharged from the hospital. The model does not describe a complete community with demographic in- and outflow and with individuals who have not been admitted to hospital. Therefore, the model is not suitable to model transmission of infection in the community.

The differential equation model is as follows:

$$\begin{aligned}
\frac{dS}{dt} &= -\beta\frac{I}{I+S}S - \alpha S + \gamma I + \epsilon V + \sigma\epsilon W,\\
\frac{dI}{dt} &= \beta\frac{I}{I+S}S - \alpha I - \gamma I + (1-\sigma)\epsilon W,\\
\frac{dV}{dt} &= \alpha S - \epsilon V + \gamma W,\\
\frac{dW}{dt} &= \alpha I - \epsilon W - \gamma W.
\end{aligned} \tag{1}$$

We refer to this model as *SIVW*. The terms of these equations are attributed to the following phenomena: term $\left(\beta\frac{I}{I+S}\right)S$ to the colonization of susceptible patients, term αS, αI to the discharge of susceptible and colonized patients, terms ϵV, ϵW to the admission of susceptible and colonized population, respectively, term $\sigma\epsilon W$ to the screening and further decolonization of colonized population on admission, term $(1-\sigma)\epsilon W$ to the admission of colonized population who are not successfully decolonized, and γI, γW to the spontaneous clearance of colonization.

All variables denote fractions of the population, so $S+I+V+W = 1$. Let $H = S + I$ denote the fraction of individuals in the hospital and $C = V + W$ the fraction of individuals in the community.

2.1. Steady states and basic reproduction number

Calculating the steady states of (1) we get

$$W^\star = \frac{\alpha I^\star}{\epsilon+\gamma} \qquad \text{and} \qquad V^\star = \frac{1}{\epsilon}\left(\alpha S^\star + \frac{\gamma\alpha}{\epsilon+\gamma}I^\star\right), \tag{2}$$

while the proportion of the population in hospital at steady state is given by

$$H^\star = S^\star + I^\star = \frac{\epsilon}{\alpha+\epsilon}. \tag{3}$$

Thus, the disease-free steady state of (1) has the form

$$E_0 = \left(\frac{\epsilon}{\epsilon+\alpha}, 0, \frac{\alpha}{\epsilon+\alpha}, 0\right) \tag{4}$$

and it exists for all values of the parameters.

In addition, using formula for W^* (2) and inserting (3) into the equation for I leads to

$$S^\star = \frac{\epsilon}{(\alpha+\epsilon)}\frac{(\gamma+\alpha)}{\beta}(1-q), \tag{5}$$

where

$$q = \frac{(1-\sigma)\epsilon\alpha}{(\epsilon+\gamma)(\alpha+\gamma)}, \quad 0 \leq q < 1, \tag{6}$$

describes the probability that an individual who left the hospital being colonized is still colonized at the next admission into hospital. Now $I^\star$ can be calculated as $H^\star - S^\star$ obtaining

$$I^\star = \frac{\epsilon}{\alpha+\epsilon}\left(1 - \frac{\gamma+\alpha}{\beta}(1-q)\right). \tag{7}$$

To have a positive steady state of (1) first we need to ensure positivity of $S^\star$ that is $q < 1$. On the other hand for $I^\star > 0$ we additionally need

$$R_0 := \frac{\beta}{(\gamma+\alpha)}\left(\frac{1}{1-q}\right) > 1. \tag{8}$$

This result for R_0 makes sense intuitively, because $\beta/(\gamma+\alpha)$ is the number of secondary infections produced by an infectious individual

during one stay in hospital, and the last term describes the sum of probabilities of still being colonized at any admission to hospital:

$$1 + q + q^2 + \cdots = \sum_{i=0}^{\infty} q^i = \frac{1}{1-q}.$$

Often R_0 is called the basic reproduction number, and in case of models with single infected compartment it is the expected number of secondary cases produced in a completely susceptible population by a typical infectious individual, and it equals to the product of the infection rate and the mean duration of the infectious period. For more complex models, having several infected compartments, the basic reproduction number can be defined as the number of new infections produced by a typical infectious individual in a whole population in a disease-free steady state. It can be analytically calculated, for details see e.g. van den Driessche and Watmough (2002), yielding formula (8).

On the other hand, the reproduction number for one hospital admission is defined as

$$R_A := \frac{\beta}{\gamma + \alpha}. \tag{9}$$

Clearly, the screening at admission can reduce the basic reproduction number R_0, i.e. when $\sigma \to 1$, q goes to zero, cf. Eq. (6). For $\sigma = 1$, we get $R_0 = R_A$. This implies that if $R_A > 1$, screening at admission cannot prevent persistent spread of pathogen within the hospital.

2.2. Stability of steady states and model dynamics

To analyse system (1) we rewrite it using $V = 1 - S - I - W$

$$\begin{aligned} \frac{dI}{dt} &= \beta S \frac{I}{I+S} - \alpha I - \gamma I + (1-\sigma)\epsilon W, \\ \frac{dW}{dt} &= \alpha I - \epsilon W - \gamma W, \\ \frac{dS}{dt} &= -\beta S \frac{I}{I+S} - \alpha S + \gamma I + \epsilon(1 - S - I - W) + \sigma\epsilon W. \end{aligned} \tag{10}$$

Theorem 2.1. *For $R_0 < 1$ steady state $e_0 = (0, 0, \bar{S})$ to system (10) is locally asymptotically stable, while for $R_0 > 1$ it is unstable.*

Proof. The Jacobian matrix for a disease-free steady state $e_0 = (0, 0, \bar{S})$ to system (10), where $\bar{S} = \epsilon/(\alpha + \epsilon)$ reads

$$J(e_0) = \begin{bmatrix} \beta - \alpha - \gamma & \epsilon(1-\sigma) & 0 \\ \alpha & -(\epsilon + \gamma) & 0 \\ -\beta - \epsilon + \gamma & -\epsilon(1-\sigma) & -(\alpha + \epsilon) \end{bmatrix} \tag{11}$$

and thus the considered characteristic equation has the following form

$$\begin{aligned} &\det\left(J(e_0) - \lambda I\right) = \\ &-(\alpha + \epsilon + \lambda)\left(\lambda^2 + \lambda(\epsilon + 2\gamma + \alpha - \beta) + (\gamma - \beta)\epsilon + \gamma(\alpha - \beta + \gamma) + \alpha\epsilon\sigma\right) \\ &= 0. \end{aligned} \tag{12}$$

Clearly, for $R_0 > 1$ inequality $\beta(\epsilon + \gamma) > (\epsilon + \gamma)(\alpha + \gamma) - (1 - \sigma)\alpha\epsilon$ holds and $e_0 = (0, 0, \bar{S})$ is a saddle point.

For $R_0 < 1$ and $\alpha - \beta > 0$, we have $\epsilon + 2\gamma + \alpha - \beta > 0$ and (12) has only one real negative root and the real parts of the remaining roots are negative. On the other hand, for $R_0 < 1$

$$(\gamma - \beta)\epsilon + \gamma(\alpha - \beta + \gamma) + \alpha\epsilon \geq (\gamma - \beta)\epsilon + \gamma(\alpha - \beta + \gamma) + \alpha\epsilon\sigma > 0$$

holds implying that

$$\gamma(\alpha - \beta + \gamma + \epsilon) + \epsilon(\alpha - \beta) > 0.$$

So for $\alpha - \beta < 0$, we have $\alpha - \beta + \gamma + \epsilon > 0$. Hence, again (12) has only one real root and the real parts of the remaining roots are negative yielding local asymptomatic stability of $e_0 = (0, 0, \bar{S})$. ■

Theorem 2.2. *For $R_0 = 1$ we observe a forward bifurcation for system (10).*

Proof. In general, due to the complex expressions, the investigation of the local stability of the endemic steady state is not an easy task. However, to investigate the nature of the bifurcation occurring at $R_0 = 1$ we use an approach based on the centre manifold theory proposed in van den Driessche and Watmough (2002) to show that there is a $\delta > 0$ such that there exists near the disease-free steady state (e_0) a locally asymptotically stable endemic steady state for $0 < \mu < \delta$. To do so, we need to investigate the signs of

$$a = \frac{v}{2} D_{xx} f(e_0, 0) w^2 = \frac{1}{2} \sum_{i,j,k=0}^{3} v_i w_j w_k \frac{\partial^2 f_i}{\partial x_j \partial x_k}(e_0, 0), \tag{13}$$

$$b = v D_{x\mu} f(e_0, 0) w = \sum_{i,j,k=0}^{3} v_i w_j \frac{\partial^2 f_i}{\partial x_j \partial \mu}(e_0, 0), \tag{14}$$

where: $f(x, \mu)$ is the right hand side of the considered system; μ — bifurcation parameter (such that for $R_0 < 1$ we have $\mu < 0$, while for $R_0 > 1$ we have $\mu > 0$ and a disease-free steady state exists for all values of μ and its stability changes at $\mu = 0$); v and w are the corresponding left and right null-vectors, respectively, chosen in such a way that $vw = 1$ and $D_x(e_0, 0) = J(e_0, 0)$. Since in our case it is inconvenient to use R_0 directly as a bifurcation parameter, we take

$$\mu = \beta - \bar{\beta}, \qquad \bar{\beta} = \alpha + \gamma - \frac{(1-\sigma)\alpha\epsilon}{(\epsilon + \gamma)} > 0. \tag{15}$$

Clearly, (10) fulfils conditions (A1)–(A5) postulated in van den Driessche and Watmough (2002) and $J(e_0)$ given by (11) has a simple zero eigenvalue for $R_0 = 1$, cf. (12). Moreover, all required second derivatives of the right hand-side of (10) evaluated at $(e_0, \bar{\beta})$ are zero except the following:

$$\frac{\partial^2 f_1}{\partial I^2}(e_0, \bar{\beta}) = -\frac{2}{\epsilon}\bar{\beta}(\alpha + \epsilon), \qquad \frac{\partial^2 f_3}{\partial I^2}(e_0, \bar{\beta}) = \frac{2}{\epsilon}\bar{\beta}(\alpha + \epsilon),$$
$$\frac{\partial^2 f_1}{\partial I \partial \beta}(e_0, \bar{\beta}) = 1, \qquad \frac{\partial^2 f_3}{\partial I \partial \beta}(e_0, \bar{\beta}) = -1.$$

Since $v_3 = 0$ (for the explanation see (van den Driessche and Watmough, 2002, Lemma 3)) and direct calculations show that v and w can be chosen in such a way that $v_1, w_1 > 0$ we get

$$a = -v_1 w_1^2 \frac{\alpha + \epsilon}{\epsilon}\bar{\beta} < 0 \quad \text{and} \quad b = v_1 w_1 \neq 0$$

implying a forward bifurcation. ■

Clearly, Theorem 2.2 shows that for R_0 we have a forward bifurcation. Moreover, for $\sigma = 1$, $R_0 = R_A$, and as long as $R_A < 1$, the disease-free steady state is locally asymptotically stable and the (positive) endemic steady state does not exist. On the other hand, for $R_A > 1$ the endemic steady state exists and gains stability while the disease-free one looses it.

In summary, the HC-model displays two types of dynamics:

1. For $R_A < R_0 < 1$ there exists only one disease-free steady state E_0 which is locally asymptotically stable. In such a case, colonization is not persistent in the hospital and will die out within infinite time horizon.
2. For $R_0 > 1$ there co-exist two steady states: disease-free E_0 (which is unstable) and endemic $E_1 = (S^*, I^*, V^*, W^*)$. Moreover
   (a) for $R_A < 1 < R_0$ the transmission in hospital during one stay is too low to lead to a persistent colonization in the hospital and the readmission of colonized patients is necessary to keep transmission going,
   (b) for $R_0 > R_A > 1$ the transmission during one hospital stay is already sufficient to lead to persistent colonization within one hospital.

3. Network model

We now extend the model to include the pathogen spread within the entire network and to understand the contribution of each hospital to this process. In particular, we will study the impact of network structure on transmission dynamics compared to an unconnected set of SIVW populations.

In reality, the hospital–community pairs (HC-pairs) do not co-exist independently. They form a healthcare system within a region or state, and they interact as patients go for treatment to different healthcare facilities. Therefore, transmission dynamics in the HC-pairs are influenced by the flow of patients through the network of hospitals. To model this process, we used a network model of healthcare systems developed in Piotrowska et al. (2020) and Piotrowska and Sakowski (2019a). We first describe the datasets used by the model, and then the structure of the simulation model.

3.1. Data description

We consider input data from two different companies to which we have access to check if the impact of the healthcare network would be similar or it would vary for different regions. Datasets used to inform the simulation model represent inter-hospital networks in the following German regions:

- Lower Saxony (LS, provided by AOK Lower Saxony company anonymized records, years 2008–2015),
- Saxony and Thuringia (ST, provided by AOK Plus company anonymized records, years 2010–2016).

Although the datasets are from the same country, they come from regions with a significantly different characteristics and history. In addition, the abbreviation AOK simply stands for *Allgemeine Ortskrankenkasse*, i.e. general regional health insurance, and it is the name of 11 independent health insurance companies in Germany.

The provided datasets consist of hospitalization records of patients insured by the respective insurance companies, and each record contains the following information: patient anonymized ID, birth year, sex, the dates of admission and discharge, medical diagnosis codes (ICD-10 codes), anonymized ID of the healthcare facility where patient is admitted, and the state where the facility is situated. In order to obtain networks that reflect realistic transfers of patients, we restrain the datasets to records from LS for AOK Lower Saxony dataset and to records from ST for AOK Plus (Piotrowska and Sakowski, 2019b; Lonc et al., 2019b,a).

The AOK Lower Saxony dataset contains 5 254 492 healthcare facility stay records, of which 4 573 584 are from the facilities located in Lower Saxony, while the AOK Plus dataset contains 4 826 823 records, of which 2 991 597 are from facilities located in Saxony and 1 566 451 are from facilities located in Thuringia. The differences between different states reflect the difference between the populations of these states. Based on census conducted by Federal Statistical Office in 2011, there were 4 056 799 people in Saxony, 2 188 589 in Thuringia and 7 777 992 in Lower Saxony. Furthermore, the data from AOK Lower Saxony concerns the eight-year period as opposed to the seven-year period in AOK Plus dataset.

Similarly, there are more healthcare facilities in Lower Saxony (223) than in Saxony (88) and Thuringia (46). For both datasets, we observe some similarities when it comes to characterizing hospitals by the number of admissions — both distributions have only one peak and it lies at interval 10^3–10^4, see Fig. 1. However, when it comes to the number of patients, the ST distribution has one great peak at interval 10^3–10^4, whereas for LS there are almost as many facilities in the interval 10^2–10^3 as in 10^3–10^4.

Both datasets have similar distributions of duration of both hospitalizations and stays at home between hospitalizations (Fig. 2). In both cases, hospitalizations with a stay duration of three days are the most common. Above that, the number of hospital stays quickly decreases with increasing length of stay. For home stays, the decrease is considerably slower and we observe some fluctuations.

Modelling transfers in created networks is based on each patient's records with overlapping stay periods. There are significant differences in the characteristics of the overlapping records between considered datasets. For LS, the overlap cases are generally more complex and therefore harder to analyse and include in the hospital network model. Furthermore, for ST the intersections are shorter — 89.9% of them last only one day, whereas for LS such cases constitutes 54% of overlaps. For further analysis of the datasets, we refer the reader to Piotrowska and Sakowski (2019b) and Lonc et al. (2019b). It should be noted that in both datasets there were several instances of facilities which were not operating through the whole period. Thus, these facilities were ignored in the simulations.

3.2. Model

Within our model, it is assumed that there are two kinds of nodes, corresponding to healthcare facilities (H-nodes) and their community nodes (C-nodes). The total number of nodes is therefore two times the number of healthcare facilities. In every node, there are two types of populations: susceptible (S) and infectious (I), like in standard simple SIS model (Bailey, 1975; Keeling and Rohani, 2011). Note that while the name *infectious* may suggest that these people are infected, it is in fact not necessary for any symptoms to occur. It is only important that these people are colonized and they may transmit the infection to susceptible population.

Since we want to model hospital-acquired infections, it is assumed that the transmission of pathogens takes place only in the H-nodes (healthcare facilities). C-nodes comprise people discharged from an associated H-node and waiting for a future admission (in perspective ranging from few days to few years). Patients waiting for a readmission to the same facility correspond to V and W populations of SIVW model, as described in Section 2. However, in C-nodes there are also patients waiting for a readmission to different facilities. The pathogen transmission dynamics in every node is governed by the SIS model, however in C-nodes we assume no further transmission — only clearance is possible. It is worth noting that C-nodes do not mean to be associated to any geographical location or proximity of the H-nodes they correspond to. Rather they are simply artificial "containers" for the patients dismissed from the hospitals. Thus, we assume that there is no exchange of population between C-nodes. Moreover, this model does not account for patients visiting the hospitals less frequently than once every few years, as their impact on pathogen transmission is negligible. In addition, for simplicity, it is assumed that the transmission/clearance parameters are the same in each class of nodes.

Exchange of populations between the nodes is assumed to take place once a day, at the same moment in the whole network, called a *transfer moment*, and we assume it is instantaneous. To summarize, the following movements are allowed by the model:

1. From a H-node to a different H-node. This case corresponds to an inter-hospital transfer, which is a direct path of pathogen spread in the healthcare system.
2. From a H-node to an associated C-node. This is a patient discharge. After a discharge, the patient always go to the C-node associated with a H-node facility.
3. From a C-node to a H-node. This is a (re-)admission. A patient may go back to the originating H-node, or to a different one.

In this setting, the path (H-node → H-node) is called a *direct transfer*, while the path (H-node → C-node → H-node) — an *indirect transfer*, as it comprises a period spent outside of healthcare facilities. For the indirect transfers, if the originating H-node is the same as the source H-node, then we call it an (indirect) *auto-transfer*. This case is similar to SIVW system dynamics. Thus, a given H-node–C-node pair (HC-pair) in

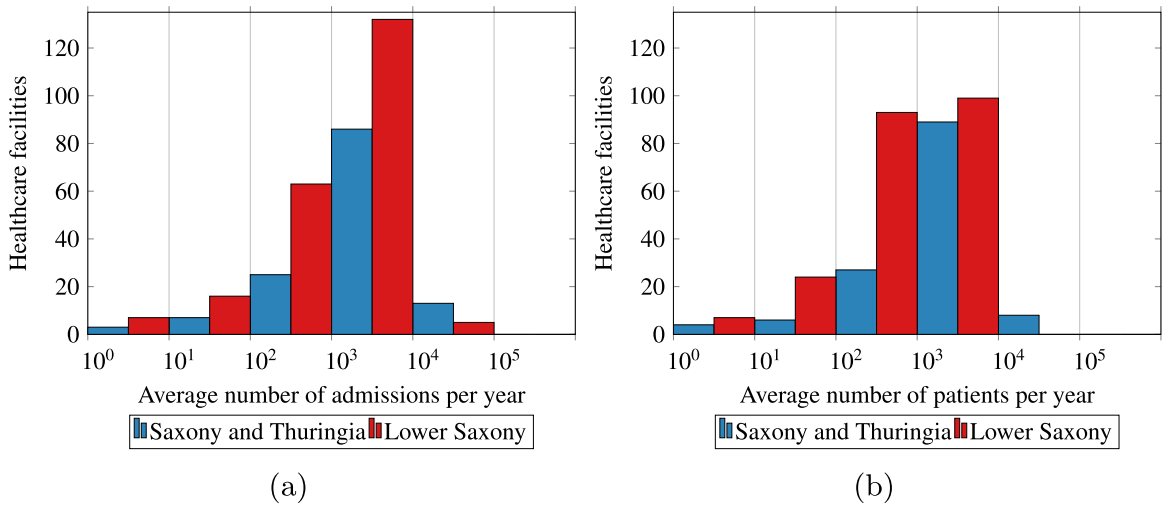

Fig. 1. Number of healthcare facilities with given average number of admissions (a) and patients (b) per year for ST (years 2010–2016, data provided by AOK Plus) and LS (years 2008–2015, data provided by AOK Lower Saxony).

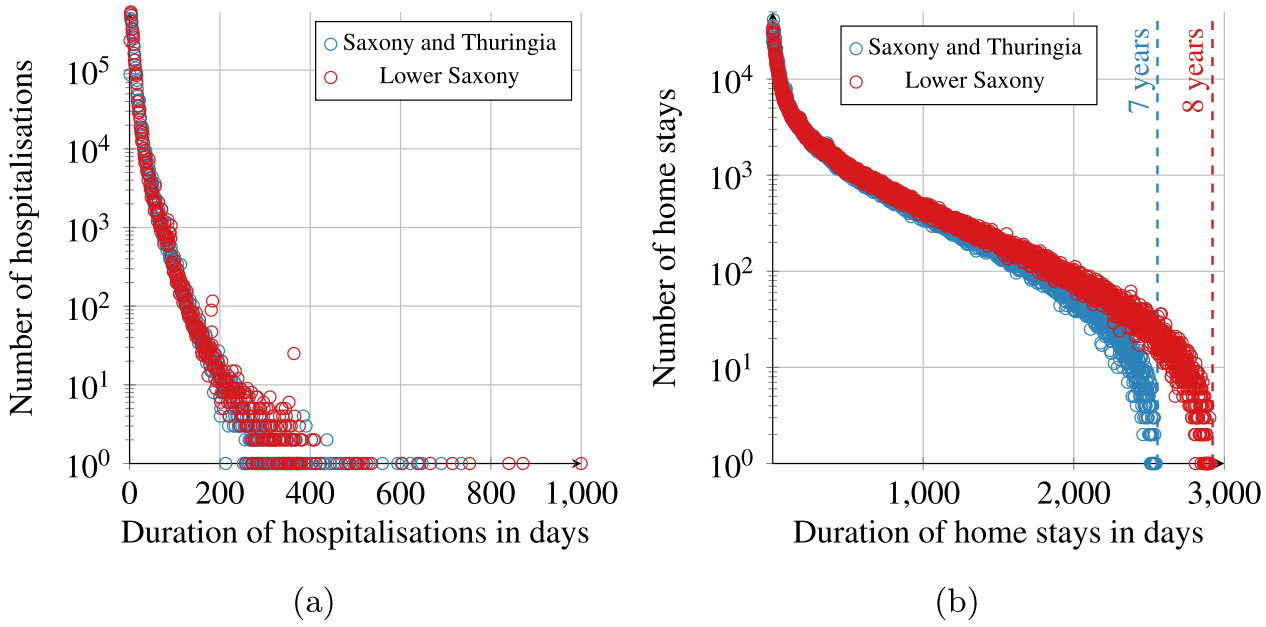

Fig. 2. Length of hospitalizations (a) and home stays (b) for LS and ST data in days. For LS data, 4 longest duration stays (1001, 1013, 2223 and 2346 days) were omitted for the visibility of the data.

this model corresponds to a single instance of SIVW system. Note that hospital ↔ community transfers in this model are discrete, and this does not pose an issue as such transfers happen quite frequently (once per day).

In our networks, nodes represent hospitals and corresponding communities. These nodes are connected via edges which represent patient movements between these nodes in each direction. The transport of patients between the nodes operates (once per day) on a Markov-chain basis, i.e. there is a non-zero probability of transfer between any two nodes connected by an edge. The edges are directional, as these probabilities are often different for opposite directions. At the transfer moment, the fraction of the populations corresponding to these probabilities are transferred.

Derived networks can be visualized by directed graphs. In Fig. 3(b) and (d), we see the visualization of the network created on the basis of the AOK Plus data. The graph is strongly connected, which means that from any node it is possible to reach every other node. The diameter of the graph is 4, so the distance between every two nodes is not greater than 4. The graph's radius is 3, meaning that there exists a node which is away from all others by no more than 3. Every node has on average 100.22 neighbours and its in-degree (the number of edges which are directed towards the node, excluding self-loops) and out-degree (the number of edges which are directed away from the node, excluding self-loops) are equal to 58.13. We also present a network containing only the healthcare facilities and direct patient transfers between them. Fig. 3(a) and (c) visualizes the graph representing the Lower Saxony network. The graph is again strongly connected, its diameter is 5 and its radius is 3. The average number of neighbours is 106.41 and the average in-degree and out-degree are 59.77.

In Fig. 4, we see the distributions of in- and out-degree respectively for hospital nodes in both networks. For these nodes, the in-degrees are generally greater than out-degrees, due to the fact that edges starting at chosen hospital represent the direct transfers to other facilities or the return to community (one node), whereas the edges directed to the chosen hospital correspond to both direct transfers and indirect transfers (edges from all community nodes). Moreover, there is no

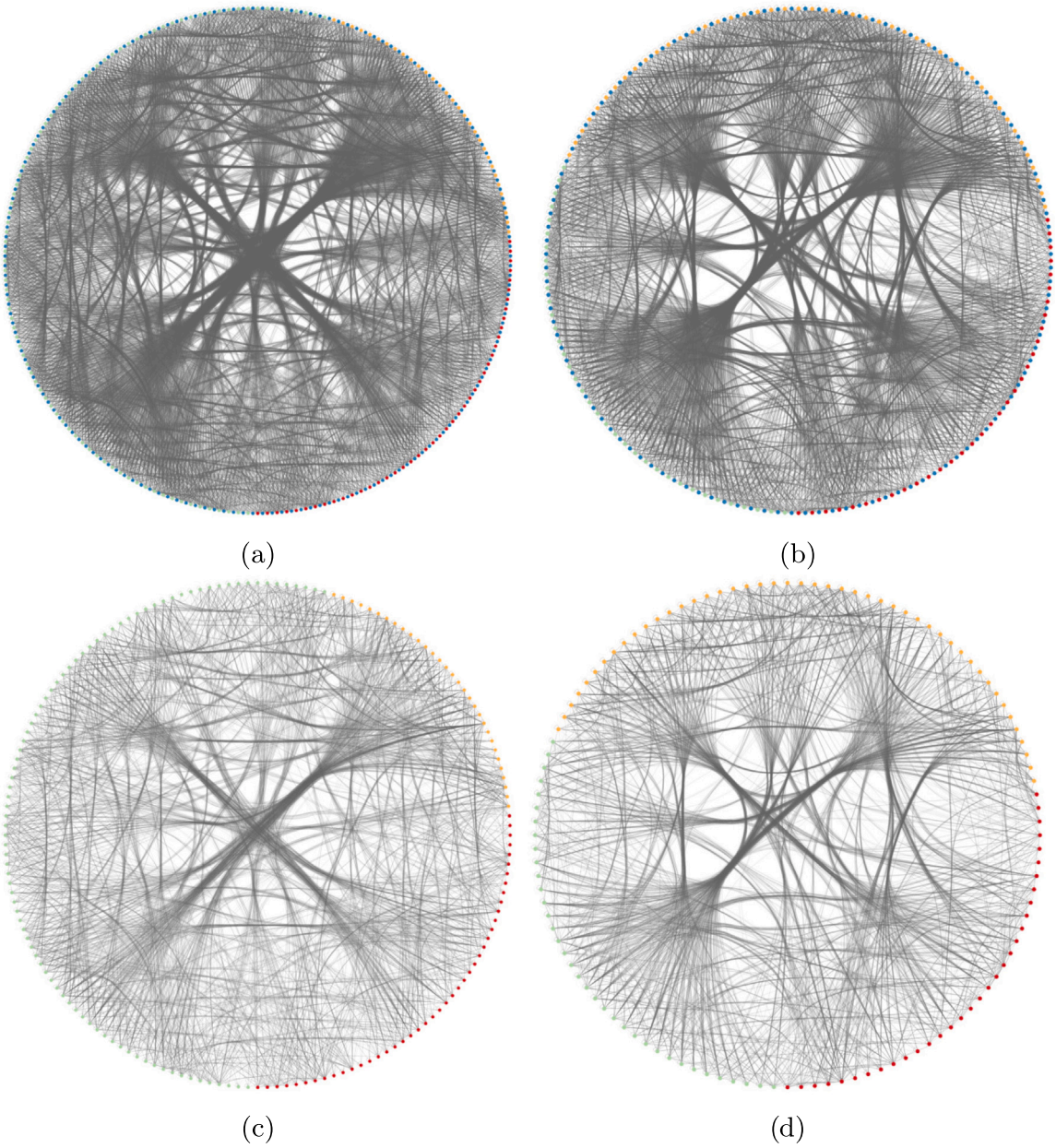

Fig. 3. Visualization of network based on: LS data (a) all nodes (c) hospital nodes only, and TS data (b) all nodes (d) hospital nodes only. The red nodes represent the H-nodes for which R_0 and R_A are greater than 1, the orange nodes represent the H-nodes for which $R_0 > 1 > R_A$, the green nodes represent the H-nodes for which R_0 and R_A are smaller than 1, while the blue ones correspond to the C-nodes. The edges represent the positive probability of transfer from one node to another and the wider the edge, the higher the probability of transfer is. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

clear dependence of in- and out-degree on R_0. Also, in Fig. 5 we see the differences in shape of distributions of in-degrees between AOK Plus and AOK Lower Saxony, which underline diversity between these networks.

3.3. Model parameters and setting

The fundamental parameters of the network model are the inter-node transfer probabilities. These probabilities are derived directly from anonymized admission/discharge records — details of this procedure may be found in Piotrowska et al. (2020), with the node sizes estimated directly form the input data.

For each node, a simple SIS model composed of system of differential equations is used to simulate the process of colonization/infection (Martcheva, 2015). Regarding the model parameters, we used the following values for H-nodes: the transmission rate $\beta = 0.029\,\text{day}^{-1}$ (Gurieva et al., 2017), the clearance rate $\gamma = 1/365\,\text{day}^{-1}$ (Scanvic et al., 2001; Donker et al., 2010, 2014). For C-nodes, we use the same clearance rate and $\beta = 0$, as no transmission in the community is assumed, as in SIVW model in Section 2.

Another important parameter in the model is the transfer intensity rate $\tau \in [0, 1]$. The extreme cases correspond to no transfers ($\tau = 0$) and full transfers ($\tau = 1$). The latter case ($\tau = 1$) simply corresponds to the undisturbed (full) network, Fig. 3, constructed from the actual datasets. It is therefore a model of healthcare system, in which HC-pairs interact with each other. On the other hand, to obtain the former ($\tau = 0$), the inter-hospital transfers were ignored. This case corresponds to isolated HC-pairs.

For any Markov-chain matrix $[a_{ij}]_{i,j\in\{1,\dots,2n\}}$, comprising the transfer probabilities between the nodes, elements a_{ij} correspond to transfer probability from ith node to jth node. Indices $1, \dots, n$ correspond to

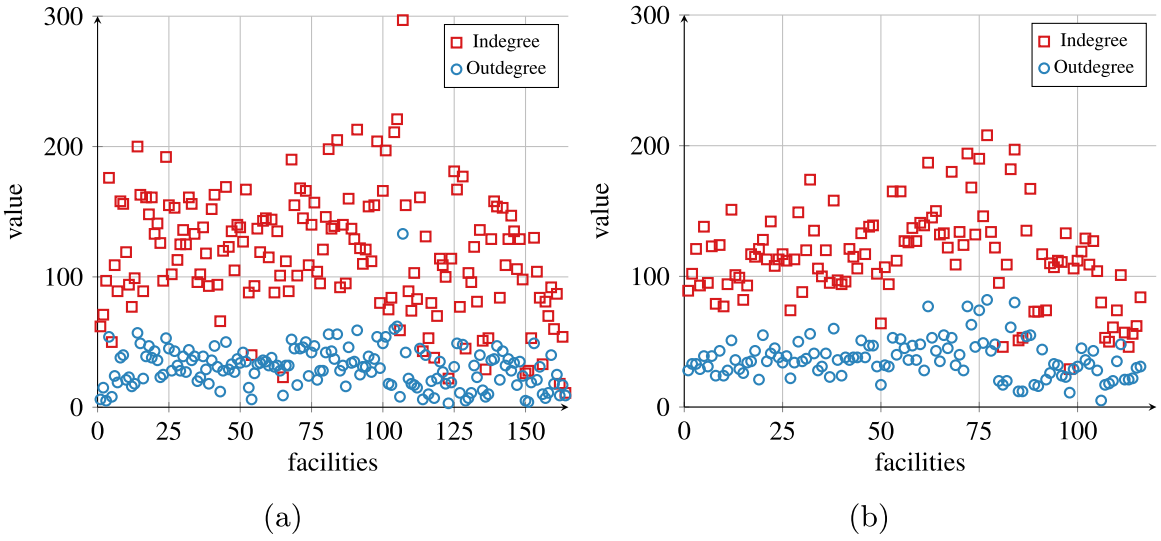

Fig. 4. In-degree and out-degree of the healthcare facility nodes sorted by the R_0 value for LS (a) and ST (b) data. The sum of in-degrees shown on the figures do not sum to the out-degrees, as only healthcare facilities (H-nodes) are present in the figures.

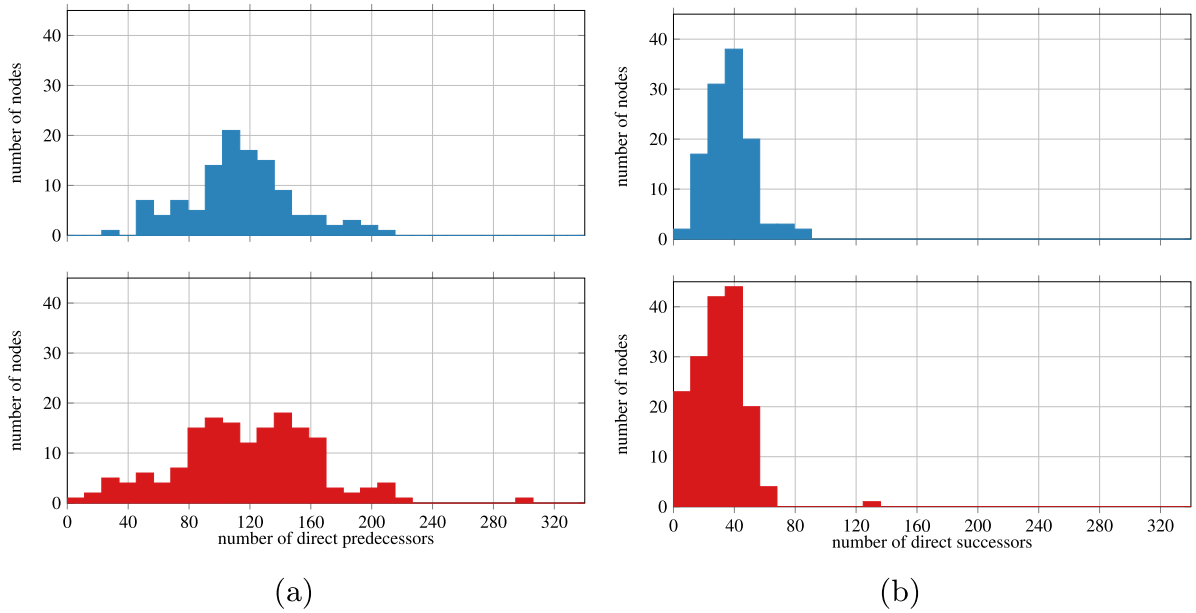

Fig. 5. In-degree (a) and out-degree (b) of the healthcare facility nodes for AOK Plus (blue) and AOK Lower Saxony (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

H-nodes, and $n+1,\ldots,2n$ to C-nodes. We assume that ith H-node corresponds to $i+n$-th C-node. Let A_{full} be a Markov-chain matrix corresponding to $\tau=1$, and let A_{auto} be a respective matrix for $\tau=0$. Then we define a matrix for any intensity $\tau \in [0,1]$ as a convex combination of these two matrices:

$$A_\tau = (1-\tau)A_{auto} + \tau A_{full}, \quad \tau \in [0,1]. \tag{16}$$

As an initial state of the simulation, 1% infectious people are assumed to be distributed uniformly within the network.

In this setting, the following aspects are considered: Do all three cases (based on R_A and R_0 values) explained in Section 2 exist in real systems? Can a healthcare system be treated as a small perturbation of system of the individual HC-pairs? What is the impact of transfers? Do the individual HC-pair properties correlate with their role in a connected system?

Thus, for further reference, we would like to distinguish three cases:

$\tau=1,\sigma=0$: Full transfers — all transfers are taken into account.

$\tau=0,\sigma=0$: Isolated HC-pairs — no transfers between HC-pairs.

$\tau=0,\sigma=1$: Isolated HC-pairs, perfect screening on admission — no transfers between HC-pairs, no pathogen transfer through C-nodes.

To calculate R_A and R_0 for each ith HC-pair, we first need to estimate α_i and ϵ_i parameters which are equal to one over average length of patient stays in hospital i and corresponding community, respectively. To estimate those values, we take diagonal elements a_{ii} and $a_{i+n,i+n}$ of A_{auto} matrix i.e. the probabilities of stay of patients in ith unit and corresponding community node, respectively. Let us define the success (at given day k after admission) as discharge of the patient from hospital i. It means that for $k-1$ days, with probability a_{ii} for each day, patient was in the hospital and then at day k, patient was dismissed with probability $1-a_{ii}$. Thus, the probability of such situation is given by $a_{ii}^{k-1}(1-a_{ii})$, which is probability mass function for the geometric distribution. Hence, the average (expected) length of patient stays in

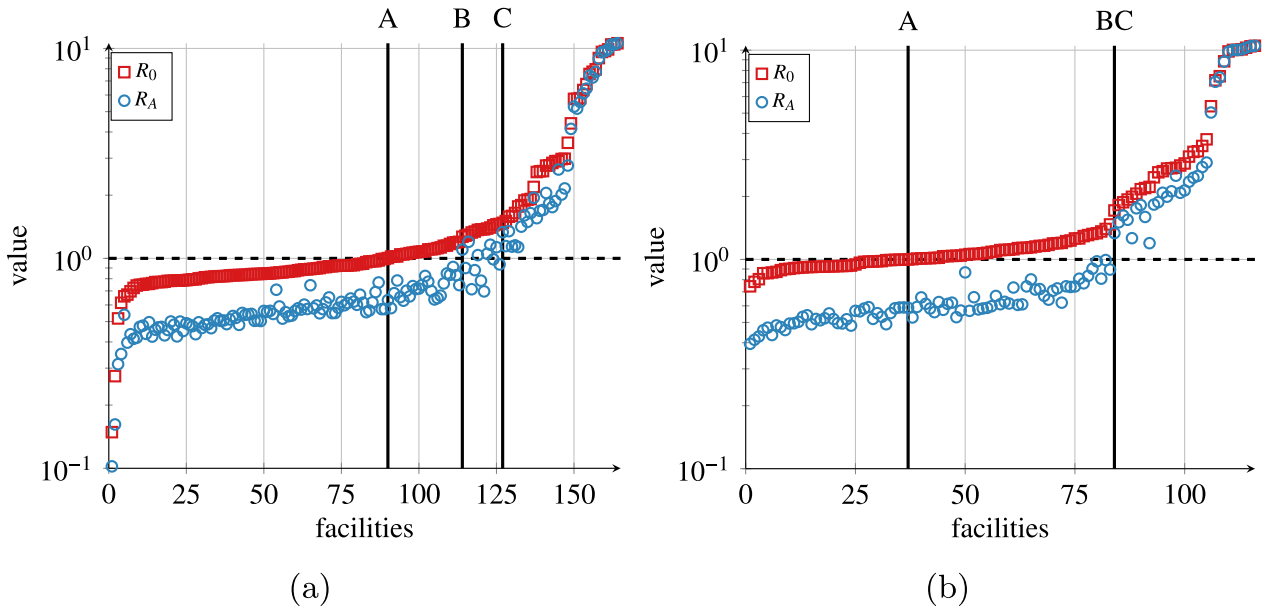

Fig. 6. Basic reproduction number R_0 and reproduction number for one hospital stay R_A given by (8) and (9) respectively, for $\sigma = 0$ and all considered healthcare facilities. Healthcare facilities are ordered by R_0 value, smallest first. α and ϵ calculated for the transfer matrix defined in (16) for $\tau = 0$: (a) AOK Lower Saxony data (LS) (b) AOK Plus data (ST). In the area on the right to A-line all units have $R_0 \geq 1$, B-line indicates first unit such that $R_A \geq 1$ while C-line represents last unit such that $R_A < 1$.

a given hospital i equals to $1/\alpha_i = 1/(1 - a_{ii})$. The same arguments holds for the community, corresponding to ith hospital, resulting in $\epsilon = 1 - a_{i+n,i+n}$.

4. Results

Let us start from the discussion of the individual HC-pair properties and their relationship to the SIVW model. For $\sigma = 0$, i.e. no screening at admission, the reproduction numbers R_0 and R_A for LS and ST cases are presented in Fig. 6, where facilities are sorted by their R_0 value. As expected, we observe correspondence of R_A and R_0. Although it cannot be exactly called monotone, the correlation is quite clear. For the LS database, $R_A < R_0 < 1$ is fulfilled for facilities numbered up to 90 (TS: 37), while $R_A < 1 < R_0$ holds for facilities from 91 up to 120 (TS: 85). For the remaining facilities $1 < R_A < R_0$ is fulfilled.

First consider the case when there is no transfer through the network, i.e. $\tau = 0$. As discussed in Section 2, $R_0 > 1$ should lead to persistent colonization of a healthcare facility, although if $R_A < 1$ the infectious patients must be readmitted to sustain the colonization. This statement holds for our simulation results of isolated HC-nodes ($\tau = 0$) presented in Figs. 7 and 8. The prevalence increases to significant levels with reproduction numbers reaching the $R_A < 1 < R_0$ regime and it increases even more when $1 < R_A < R_0$.

Further analysis of $\tau = 0, \sigma = 1$ case reveals that the colonization within $R_A < 1 < R_0$ regime is indeed due to readmission of colonized patients, as these facilities do not reach colonized state without community transmission. Nevertheless $1 < R_A < R_0$ facilities remain colonized, mostly with rather high prevalence level.

The interesting phenomenon may be observed for high R_0 or R_A values. Prevalence in these facilities remain very high (80% and more) but the colonization rates in C-nodes can in fact be low. This effect may be attributed to the very long average length of stays in these facilities, so that the dismissed patient number is too low to affect prevalence of communities significantly. In fact, transfers to other hospitals are important factor governing the average length of stay in most of these facilities, which decrease it significantly.

To estimate the impact of transfers, we increase τ (cf. Figs. 7 to 9). The prevalence pattern changes significantly, as the colonized patients are distributed through all the facilities. The distribution is not uniform, in most cases it stays below 10%. Let us focus on $\tau = 1$. We do not observe a straightforward dependence of facility prevalence on the reproduction number R_0 anymore. However, some features are preserved, as high prevalence in facility/community is present for $1 < R_A < R_0$ facilities. Otherwise it stays on low level.

The final result of this simulation, which is perhaps slightly surprising, is that increasing the transfer intensity does not result in increase of the system-level prevalence, both in sense of healthcare facilities and community (see Fig. 10). Increasing transfers from $\tau = 0$ may initially result in some prevalence increase, but then it decreases until $\tau = 1$, when prevalence reaches about 6% for both LS and TS. Generally increasing the transfer intensity promotes lower prevalence, although the healthcare system is affected more than the community.

In Fig. 11, we present the difference in prevalence for full hospital network ($\tau = 1$) and decoupled HC-pairs ($\tau = 0$). In both cases, for units with $R_0 < 1$ we observe small increase in the prevalence. On the other hand, for most units with $R_0 > 1$ we observe decrease, which is more pronounced for facilities with greater R_0. Interestingly, for units with $R_A > 1$ there appears a strong diversity, although we see decrease in the prevalence due to the network effect. Additional investigation of the difference in final prevalence in H-nodes depending on their in-degrees and out-degrees shows small positive correlation, cf. Fig. 12, however obtained results are not significant from the statistical point of view apart from in-degrees, which show weak positive correlation with the difference between prevalences for both networks.

To conclude, the presented results suggest that the dynamics in the transfer network is much more than a small perturbation of the dynamics observed for isolated facility/community pairs. While for many nodes this coupling may be the most significant effect governing their prevalence, clearly we also observe opposite behaviour. Still, the analysis of SIVW system properties is important for understanding the dynamics of the entire system, as by comparison of reproduction rates we may identify the nodes with risk of high prevalence. This knowledge may be a basis of a future system-level infection-control strategy.

Moreover, in Figs. 13 and 14 we present changes of the prevalence and respectively the final prevalence for decoupled HC-pairs model with very effective decolonization of all patients that are screened at admission ($\sigma = 1$). Comparing to the results without decolonization, we note that in for LS and ST networks, units on the left of B-line do not have colonized patients or their percentage is negligible. On the other hand, for the units on the right of C-line we observe significant proportion of colonized patients.

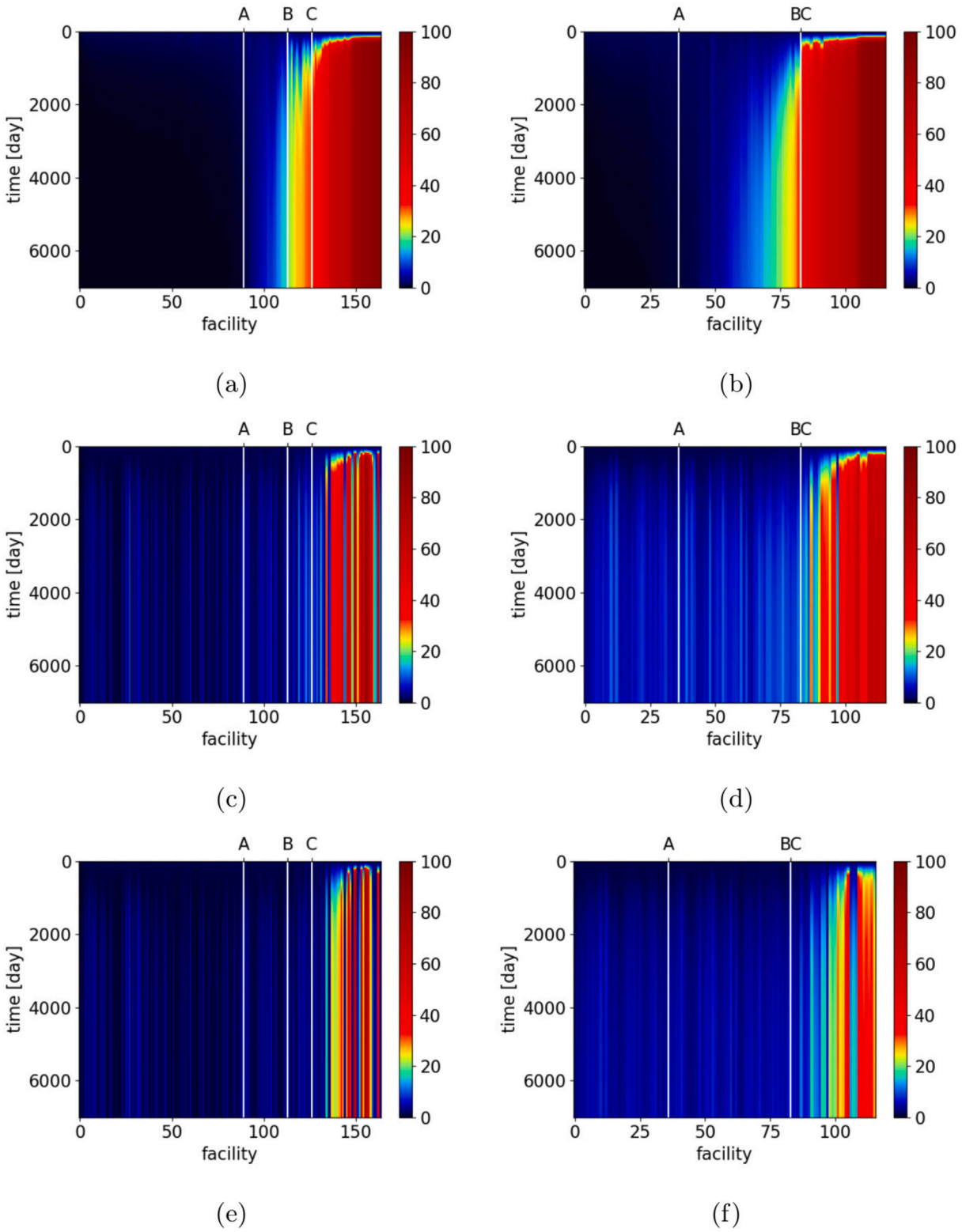

Fig. 7. Prevalence (indicated by colour) in healthcare facilities versus time for $\sigma = 0$: (a) for AOK Lower Saxony data (LS), $\tau = 0$, (b) for AOK Plus data (ST), $\tau = 0$, (c) for AOK Lower Saxony data (LS), $\tau = 1/2$, (d) for AOK Plus data (ST), $\tau = 1/2$, (e) for AOK Lower Saxony data (LS), $\tau = 1$, (f) for AOK Plus data (ST), $\tau = 1$. The facilities are sorted by basic reproduction number R_0 given by (8), smallest first. In the area on the right to A-line all units have $R_0 \geq 1$, B-line indicates first unit such that $R_A \geq 1$ while C-line represents last unit such that $R_A < 1$. On the colour bar the percentage of infectious individuals is presented. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

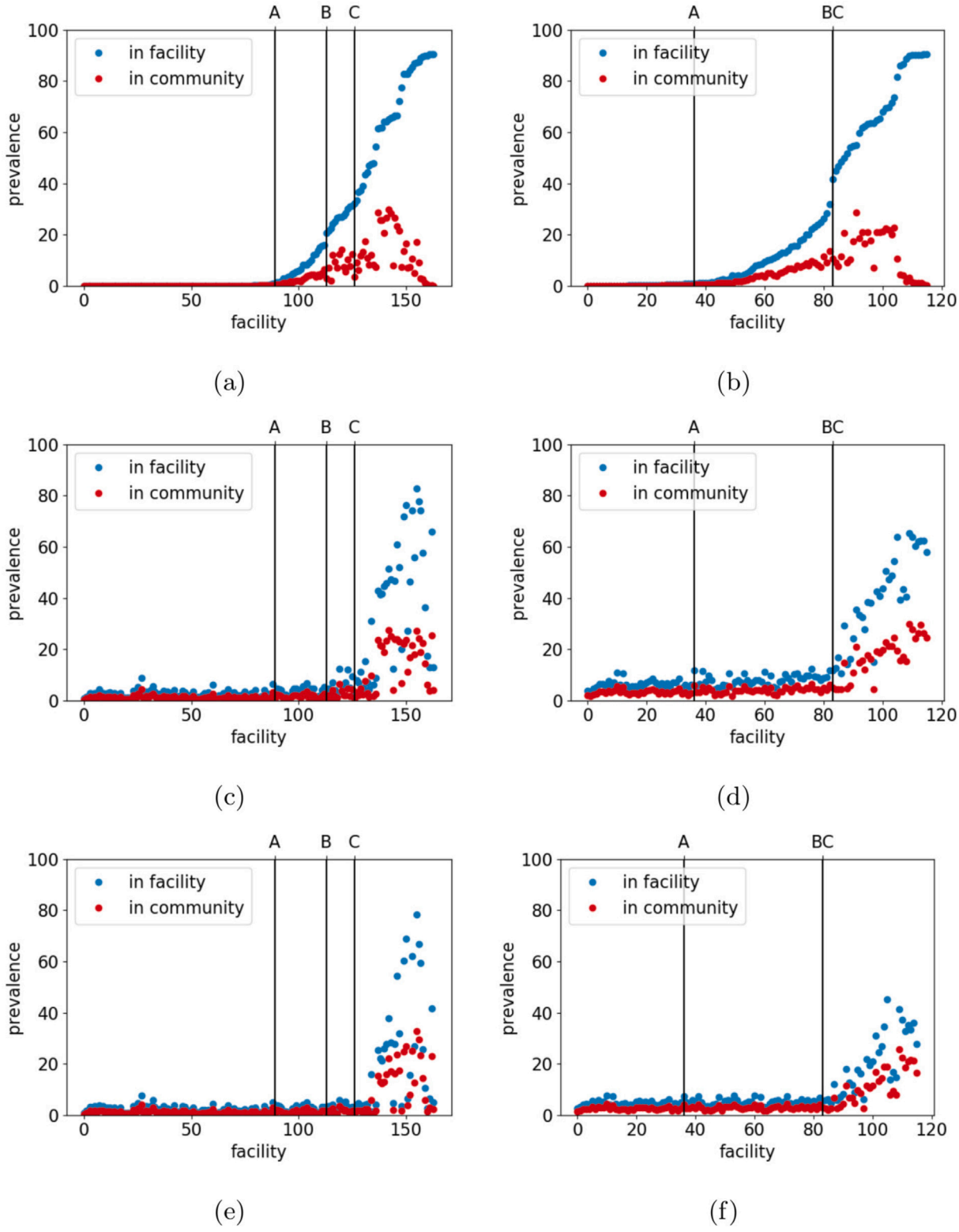

Fig. 8. Prevalence in healthcare facilities at the end of simulation for $\sigma = 0$: (a) for AOK Lower Saxony data (LS), $\tau = 0$, (b) for AOK Plus data (ST), $\tau = 0$, (c) for AOK Lower Saxony data (LS), $\tau = 1/2$, (d) for AOK Plus data (ST), $\tau = 1/2$, (e) for AOK Lower Saxony data (LS), $\tau = 1$, (f) for AOK Plus data (ST), $\tau = 1$. The facilities are sorted by basic reproduction number R_0 given by (8), smallest first. In the area on the right to A-line all units have $R_0 \geq 1$, B-line indicates first unit such that $R_A \geq 1$ while C-line represents last unit such that $R_A < 1$.

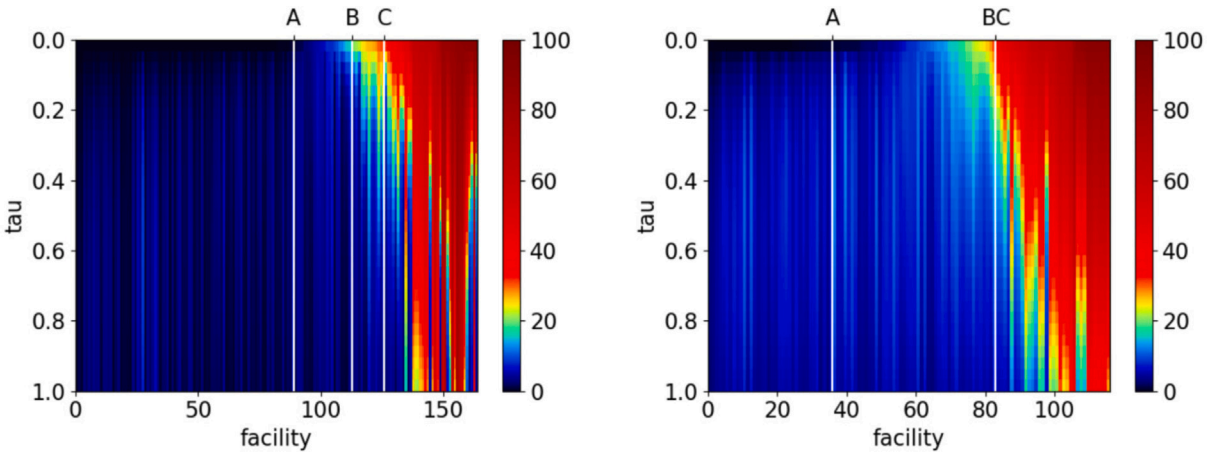

Fig. 9. Prevalence (indicated by colour) in healthcare facilities at the end of simulation versus τ (where $\sigma = 0$) for: (a) for AOK Lower Saxony data (LS) (b) for AOK Plus data (ST). On the colour bar the percentage of infectious individuals is presented. In the area on the right to A-line all units have $R_0 \geq 1$, B-line indicates first unit such that $R_A \geq 1$ while C-line represents last unit such that $R_A < 1$. On the colour bar the percentage of infectious individuals is presented. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

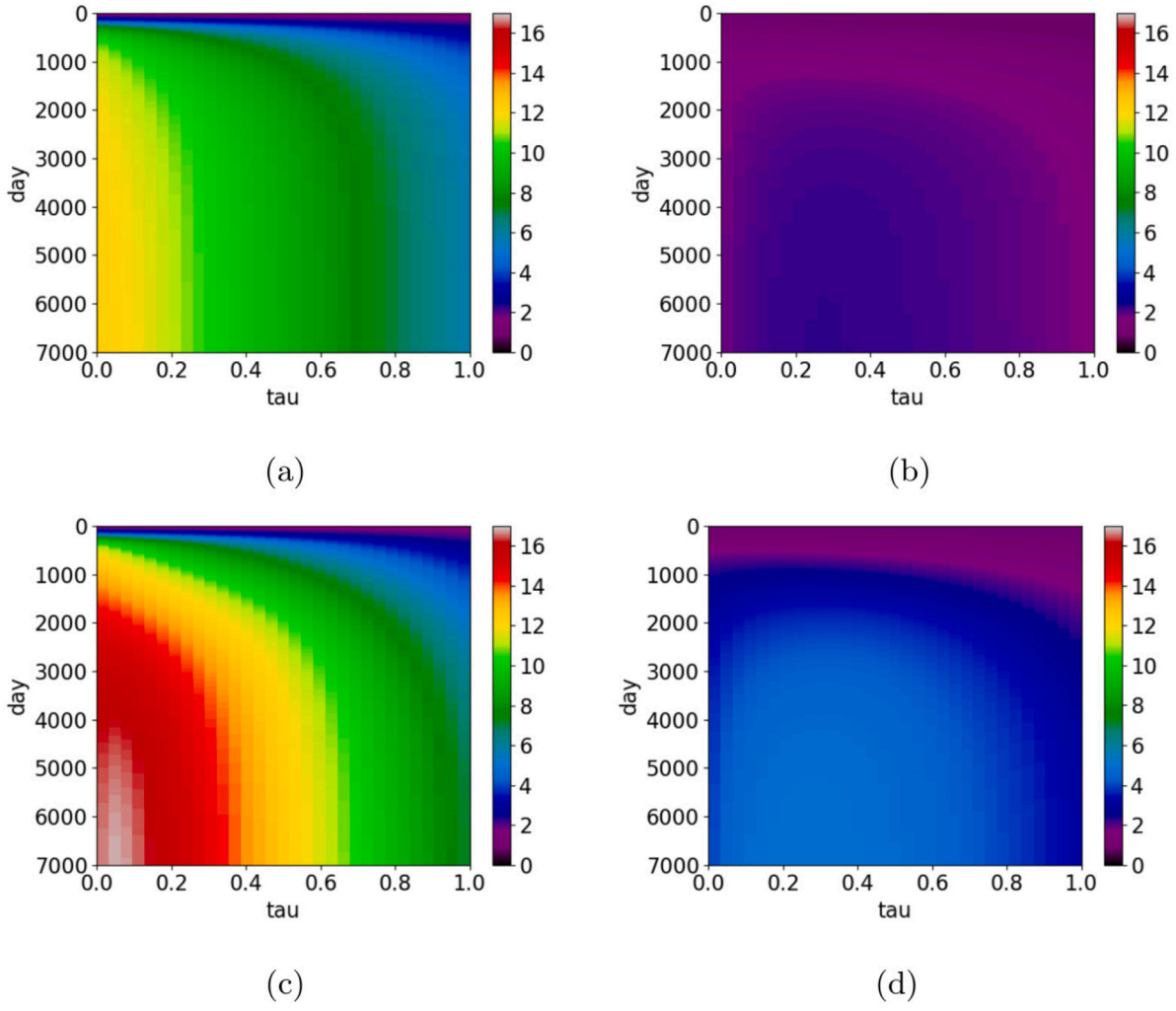

Fig. 10. System-level prevalence for the different values of τ in the transfer matrix given by (16) for $\sigma = 0$ and for different times for: (a) hospitals and (b) community nodes for AOK Lower Saxony network model (LS); (c) hospitals and (d) community nodes for AOK Plus network model (ST). On the colour bar the percentage of infectious individuals is presented. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

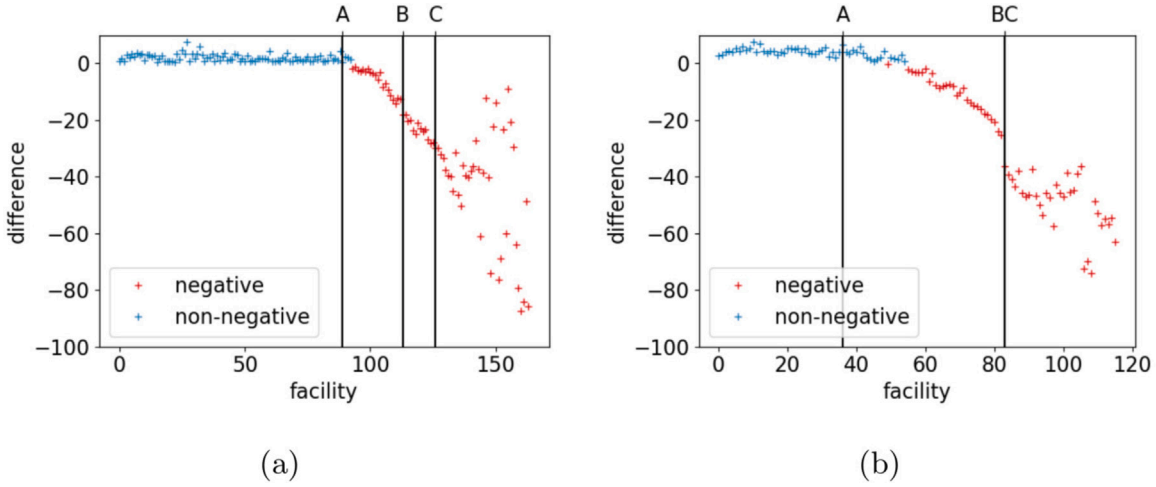

Fig. 11. Difference between prevalence in healthcare facilities between cases $\tau = 1$ and $\tau = 0$, both for $\sigma = 0$. Negative values correspond to decrease in prevalence due to network effects: (a) for AOK Lower Saxony data (LS), (b) for AOK Plus data (ST). The facilities are sorted by their basic reproduction numbers R_0 given by (8), smallest first. In the area on the right to A-line all units have $R_0 \geq 1$, B-line indicates first unit such that $R_A \geq 1$ while C-line represents last unit such that $R_A < 1$.

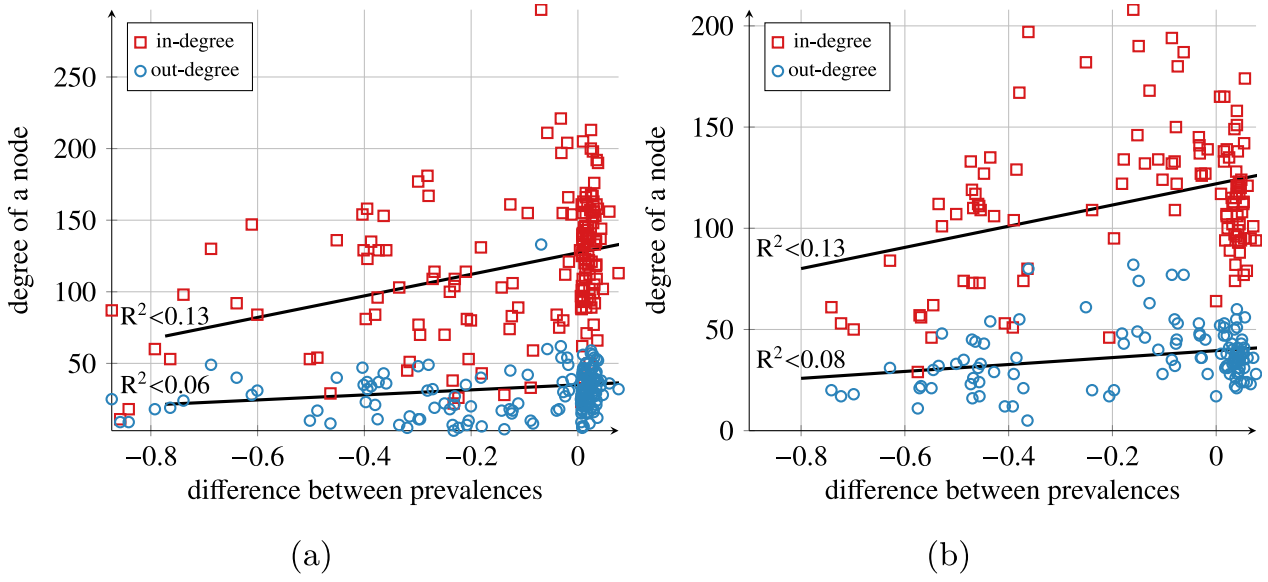

Fig. 12. Difference between prevalence in healthcare facilities between cases $\tau = 1$ and $\tau = 0$, both for $\sigma = 0$ for different hospitals showing the in-degree and out-degree of H-nodes. Negative value corresponds to decrease in prevalence due to network effect. The solid lines depict the regression lines, coefficients of determination (R^2) are estimated. Results for (a) AOK Lower Saxony data (LS), (b) AOK Plus data (ST).

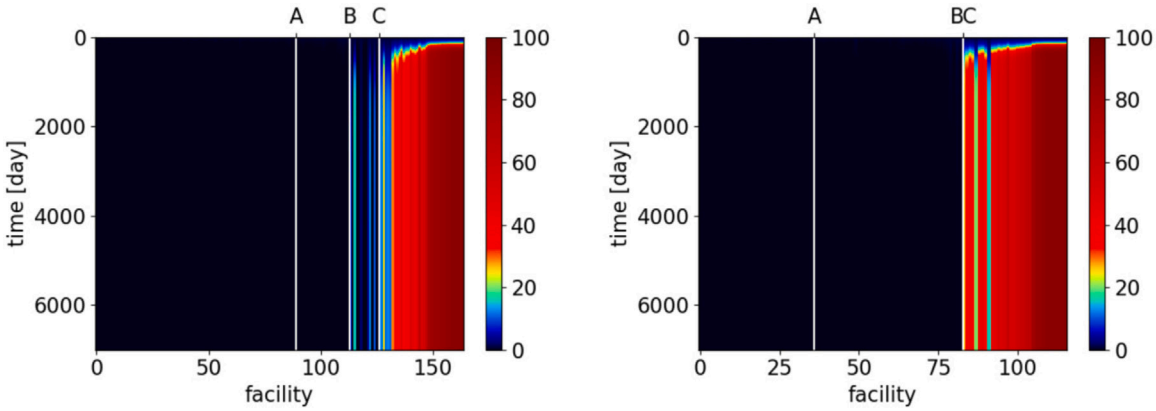

Fig. 13. Prevalence (indicated by colour) in healthcare facilities versus time for $\tau = 0$, $\sigma = 1$. The facilities are sorted by basic reproduction number R_0 given by (8), smallest first: (a) for AOK Lower Saxony data (LS) (b) for AOK Plus data (ST). In the area on the right to A-line all units have $R_0 \geq 1$, B-line indicates first unit such that $R_A \geq 1$ while C-line represents last unit such that $R_A < 1$. On the colour bar the percentage of infectious individuals is presented. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

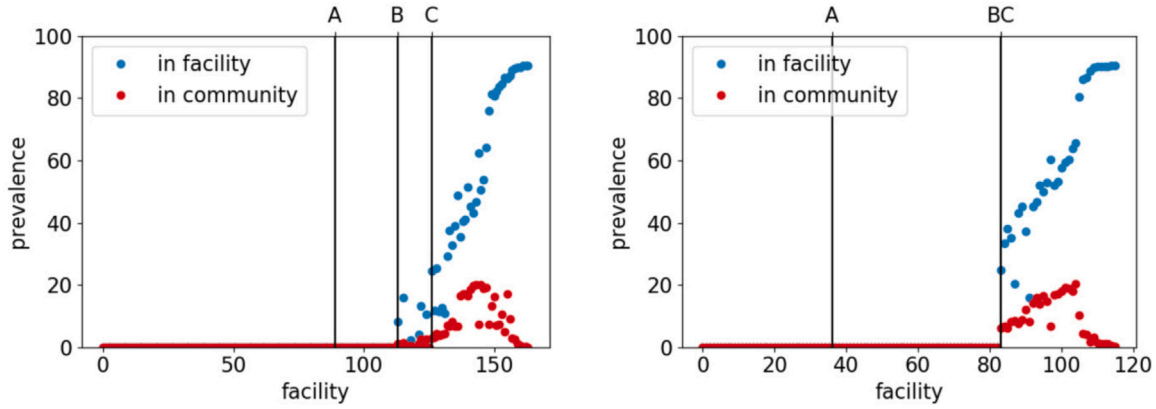

Fig. 14. Prevalence in healthcare facilities at the end of simulation for $\tau = 0$, $\sigma = 1$. The facilities are sorted by basic reproduction number R_0 given by (8), smallest first: (a) for AOK Lower Saxony data (LS) (b) for AOK Plus data (ST). In the area on the right to A-line all units have $R_0 \geq 1$, B-line indicates first unit such that $R_A \geq 1$ while C-line represents last unit such that $R_A < 1$.

5. Summary and discussion

In this paper, a hospital–community pair (HC-pair) model is proposed for the spread of resistant pathogens in a network of hospitals. It is based on the susceptible–infectious–susceptible (SIS) type differential equation model, used for patients of a hospital and an associated population — a community of potential patients of this facility. The pathogen dynamics in these groups are governed by a SIS transmission process, under the assumption that there is no transmission of pathogens in the community. Then, additional terms are added to couple the hospital SIS and community SIS, which correspond to admission and discharge of patients.

The analysis of this system reveals that depending on the model parameters (transmission rate, clearance rate, admission rate and discharge rate), there exist two possible cases: either there is only one, stable steady disease-free state, or there are two steady states: unstable disease-free state and stable endemic state. In the former case, even if initially there is a high prevalence among the populations, it will converge asymptotically to zero with time. In the latter case, the disease will not die out and there will always be certain number of colonized patients, whenever the pathogen is introduced to the system.

The dynamics of the system are governed by two threshold quantities, namely the single admission reproduction number R_A and the basic reproduction number R_0. The former describes the number of secondary cases caused by one infected individual during a single hospital stay, while the latter is the number of secondary cases caused during the entire infectious period, which may comprise more than one stay in the hospital. In situations, where $R_A < 1 < R_0$, the endemic state is only possible through readmissions of colonized patients into the hospital, i.e. the readmission from the community is then necessary to keep transmission on-going.

After connecting the HC-pairs into a network of hospitals with transfers between them, there is a flow of colonized patients between the HC-pairs. This leads to an inflow of colonization into nodes that have a stable disease-free state and we therefore see low prevalence in these nodes, but because there is not much transmission within the nodes, prevalence stays low. In nodes where $R_0 > 1$, endemic prevalence establishes itself independent of inflow from outside. These nodes are the source of overall endemic prevalence in the system.

To study these dynamics based on data from a real hospital network, we used network models of healthcare systems of Lower Saxony region (LS) and Saxony and Thuringia regions (ST), derived from anonymized records of insurance companies AOK Lower Saxony and AOK Plus, respectively. The analysis of patient transfers within these networks allowed us to estimate reproduction numbers for the isolated HC-pairs. In both networks, we find a nonzero representation of all cases predicted by the theory. The results of the simulations agree with the theoretical characterization. Moreover, by preventing the readmission of the infectious patients, the persistent colonization was removed from facilities with stable endemic state, but $R_A \leq 1$. This result confirms that in these HC-pairs, the readmission of colonized people is indeed necessary to sustain the disease. On the other hand, facilities with $R_A > 1$ remain colonized even in this case, as predicted.

Finally the individual HC-pairs were coupled together by the inter-facility transfers, and the patients within the model were allowed to go to different facilities. Various rates of transfers between HC-pairs were studied, ranging from decoupled pairs to fully coupled, as defined by the data. These simulations reveal that the impact of the healthcare network on the HC-pairs is significant. The endemic state is introduced to almost all facilities, although the prevalence is mostly low, below 10%. This behaviour is observed even if the amount of transfers is reduced significantly when compared to the actual data. However, no new high-prevalence endemic states are introduced by network effect. On the other hand, we observe many facilities with high prevalence in isolated case, which decreases significantly when the coupling is introduced.

These observations can be explained based on the differences between facilities in their values of R_A and R_0. These differences occur due to the differences in the average length of stay of patients in hospitals and the communities: if patients stay longer, R_A is higher, and if they are readmitted more frequently, the value of R_0 is higher. We assumed here that the transmission rate β is the same for all hospitals, because we had no hospital-specific information on this parameter. However, in reality there may also be differences between hospitals in their transmission rates, which would then also affect R_A and R_0. In the simulated dynamics we clearly observed differences in prevalence between the three groups of hospitals distinguished by whether their threshold values lie above or below 1. Hospital–community pairs with both thresholds below 1 have low prevalence, even if they receive colonized patients from other hospitals. Hospital–community pairs with one or both thresholds above 1 have high to very high prevalence and act as sources for the endemic prevalence in the entire network. For HC-pairs with $R_A < 1 < R_0$, prevalence is in the medium range and reducing readmission rate would suffice to bring prevalence down to low levels.

At the level of the entire network we observe that with increasing transfer rates, the system-level prevalence decreases. That result seems to be surprising at first, as we would expect the increased transfer rate to improve transmission of the disease. However, it can be explained by the effect of dilution of prevalence, when patients move from facilities with a high R_0 to those with a low R_0. In the latter, transmission chains are stopped and do not lead to many secondary cases. Conversely, if a colonized patient moves from a low R_0 to a high R_0 hospital, that patient will not add much to the already high prevalence. So in total,

transmission is reduced by moving colonized patients from high risk facilities to lower risk facilities.

However, it seems that there are some healthcare facilities in systems under consideration, which do not have a significant coupled population base. They mostly admit patients associated with different facilities. When the transfers are removed from the model, they manifest a very long average stay length, which result in high prevalence. If the coupling with other HC-pairs is restored, their prevalence is much lower.

The strength of this study is that it combines a relatively simple transmission model for single hospital–community pairs with a complex network model based on data from a real hospital network. This way, it is possible to compute reproduction numbers, which can then be used to interpret the dynamics of pathogen transmission observed in the network of hospitals. The impact of patients' transfers on the dynamics in the entire system can be studied by comparing the fully connected system to the system of unconnected HC-pairs, which is fully analytically tractable. A limitation of the study is that we did not have colonization data from the hospitals in the network, so transmission parameter values had to be taken from published literature. Although we did take into account differences between hospitals in their average length of stay, there may be many other factors that we did not have information about and could not have considered, such as: differences in morbidities of patients, implemented infection prevention and antibiotic use. Nevertheless, our results clearly demonstrate how transmission dynamics in a network of hospitals are governed by the contributions of all hospital–community pairs, and how these can be viewed as sources or sinks in the entire flow through the network.

Our results have some implications for infection prevention in healthcare systems, where hospitals are connected via patient transfers. It is important to realize that even with the most effective prevention strategies within a single hospital, readmissions of patients from other hospitals form a continuous risk of new outbreaks. Within the entire network, there may be hospitals that are a continuous source of transmission for the entire hospital network, and hospitals with low prevalence are most at risk by importation from those sources. Reducing transfers between hospitals will benefit low prevalence hospitals by reducing their risk of importation, but it will not change much in high prevalence hospitals. The latter can only reduce their prevalence by reducing readmission rates and reducing transmission within the hospital. Therefore, screening of patients who come from other hospitals at admission may be an effective strategy for hospitals with low prevalence, but not for those with medium and high prevalence. For those with medium prevalence, screening of both patients transferred from other hospitals and those readmitted from the community may suffice to reduce prevalence. For high prevalence hospitals, only improvement of within-hospital infection prevention can help to reduce prevalence.

CRediT authorship contribution statement

M.J. Piotrowska: Conceptualization, Formal analysis, Methodology, Investigation, Project administration, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **K. Sakowski:** Conceptualization, Data curation, Formal analysis, Methodology, Investigation, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **A. Lonc:** Data curation, Investigation, Validation, Visualization, Writing - review & editing. **H. Tahir:** Conceptualization, Validation, Writing - review & editing. **M.E. Kretzschmar:** Conceptualization, Investigation, Methodology, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This publication was made possible by grants from following national funding agencies: National Science Centre, Poland, Unisono: 2016/22/Z/ST1/00690 (University of Warsaw, Faculty of Mathematics, Informatics and Mechanics, Institute of Applied Mathematics and Mechanics); and the ZonMw Netherlands grant number 547001005 (Julius Centre, University Medical Centre Utrecht) within the 3rd JPI-EC-AMR framework (Joint Programming Initiative on Antimicrobial Resistance) cofound grant no 681055 for the consortium EMerGE-Net (Effectiveness of infection control strategies against intra- and inter-hospital transmission of MultidruG-resistant Enterobacteriaceae). We thank the AOK Lower Saxony and AOK Plus for providing anonymized record data. We would like also to express our thanks to Prof. Rafael Mikolajczyk, Prof. Andre Karch and Dr. Johannes Horn for substantive discussions.

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