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The role of intra and inter-hospital patient transfer in the dissemination of heathcare-associated multidrug-resistant pathogens

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ABSTRACT

Healthcare-associated infections cause significant patient morbidity and mortality, and contribute to growing healthcare costs, whose effects may be felt most strongly in developing countries. Active surveillance systems, hospital staff compliance, including hand hygiene, and a rational use of antimicrobials are among the important measures to mitigate the spread of healthcare-associated infection within and between hospitals. *Klebsiella pneumoniae* is an important human pathogen that can spread in hospital settings, with some forms exhibiting drug resistance, including resistance to the carbapenem class of antibiotics, the drugs of last resort for such infections. Focusing on the role of patient movement within and between hospitals on the transmission and incidence of enterobacteria producing the *K. pneumoniae* Carbapenemase (KPC, an enzyme that inactivates several antimicrobials), we developed a metapopulation model where the connections among hospitals are made using a theoretical hospital network based on Brazilian hospital sizes and locations. The pathogen reproductive number, R_0 that measures the average number of new infections caused by a single infectious individual, was calculated in different scenarios defined by both the links between hospital environments (regular wards and intensive care units) and between different hospitals (patient transfer). Numerical simulation was used to illustrate the infection dynamics in this set of scenarios. The sensitivity of R_0 to model input parameters, such as hospital connectivity and patient-hospital staff contact rates was also established, highlighting the differential importance of factors amenable to change on pathogen transmission and control.

1. Introduction

Healthcare-associated infections (HAIs) are those absent at the time of patient admission but acquired during the stay in a hospital. Occurrence of HAI cases is generally associated with invasive medical procedures, hospital crowding, inadequate hygiene protocols, status of patient's immune system, prolonged stay in intensive care units, and routine use of antimicrobial agents. The common pathogens causing HAIs are viruses, bacteria and fungi. These infections increase patient morbidity and mortality, and impose healthcare costs (Zimlichman et al., 2013). In Europe and North America between 5% and 10% of all hospitalizations result in HAI while in other countries this percentage is up to 40% (Bereket et al., 2012; Allegranzi et al., 2011).

Ninety percent of HAIs are caused by Gram- positive and Gram-negative bacteria, and occur in Intensive Care Units (ICUs) where the severity of illness of patients, the extensive use of wide-spectrum antibiotics and invasive procedures promote the emergence and spread of resistance. As a consequence, it is estimated that 50–60% of HAIs are caused by antibiotic-resistant pathogens (Khan et al., 2015). These infections can spread in hospital populations by contact between undiagnosed, infected hospital staff and patients, and also by patient contact with infected fomites (World and Health Organization). Among the bacterial HAIs, *Klebsiella pneumoniae* is the most prevalent opportunistic pathogen.

In 1990 a resistant strain of this bacteria called *K. pneumoniae* Carbapenemase (KPC) was isolated in North Carolina, United States (Yigit et al., 2001). This drug resistant form of the bacteria subsequently spread rapidly throughout the Northeast United States causing outbreaks in New York and New Jersey. International patient transfer is speculated to have introduced KPC to hospitals in Israel, Greece and Columbia. This bacteria is now endemic in the United States, Israel, Greece, Italy and Brazil (Nordmann and Poirel, 2014). The resistance gene spreads both clonally and by horizontal gene transfer (Robilotti and Deresinski, 2014). A combination of different antimicrobial agents

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is required to successfully treat these infections, as opposed to monotherapy, which is associated with selection for resistance (Robilotti and Deresinski, 2014). Additionally, *K. pneumoniae* is a key trafficker of several drug resistance genes between bacterial species underscoring its importance in the ongoing antimicrobial resistance crisis (Wyres and Holt, 2018).

Mathematical models have been used to assess the effectiveness of control strategies for HAIs, and to study the development of bacterial resistance. In Grundmann et al. (2002), a stochastic model was fitted to a set of data collected in an ICU that reported the incidence of *Staphylococcus aureus*. The model considers two kinds of individuals, the patients and the staff, which may be either uncolonized or colonized. During the period of collecting data, the authors observed that, on average, 59% of the contacts between staff and patients were followed by hand hygiene. Moreover, the study showed that environmental contamination is limited, and predicted that an improvement of 12% in hand hygiene following contact could stop infection transmission by reducing the R_0, the pathogen basic reproductive number, to less than 1. Similar results were obtained in a generalized stochastic framework with many compartments, that performed efficiently provided the number of state variables was not too high (López-García and Kypraios, 2018).

van Kleef et al. (2017) proposed a deterministic compartmental model to assess how hand hygiene intervention may prevent infections by both drug resistant and drug sensitive bacteria. The model captured the transmission of strains in both hospital and community settings. In the former, transmission was assumed to occur through contaminated hands of healthcare workers (HCW) and once hand hygiene was performed, the contamination was cleared. They further assumed that resistant strains are better adapted to the hospital environment and sensitive strains are better adapted to community environment, based on the presence and absence of drug pressure in the two environments. They found that hand hygiene intervention targeting only one of the environments strongly affects the better-adapted strain. Moreover, the flux of patients between community and hospital environments maintained the frequency of the sensitive strain, while the hand hygiene limited the spread of the resistant strain.

Recently, mathematical models have been addressing the importance of hospital networks on the spread of healthcare-associated infections. Donker et al. (2012) used an agent-based model to study the spread of a nosocomial infection on the British hospital network. Using data from the health care system on patient admissions, discharges and transfers for each hospital, they estimated the probability that a patient carries the infection from one hospital to another. This estimate takes into account several factors: the probability of acquiring the infection which depends on the length of stay; the probability of transmitting the infection, which depends on the length of stay following readmission; and the probability of being infected upon readmission. They showed that in order to contain the spread of infection, the hospitals must be seen as part of a connected network and not only as an isolated unit.

Karkada et al. (2011) presented a network model based on the national information of direct ICU patient transfers in the USA. In order to analyse various control strategies, they allocated arbitrary units of infection control to the hospitals. Each unit was assumed to reduce the transmission probability by 25% and if a hospital received more than one unit, the reduction was cumulative. They compared three different strategies for unit allocations in the network: random allocation, specific allocation given by the degree-centrality (a measure of how many hospitals are directly connected to the focal hospital by patient transfer) and specific allocation given by the betweenness-centrality (a measure of how often the shortest network path between two hospitals passes through the focal hospital). Allocation by betweenness-centrality performed best in mitigating transmission in the network, and once optimized, this strategy was evaluated to be sixteen times more efficient than random allocation.

The control of emergence and spread of new resistance phenotypes (such as KPC) in Brazil is challenging, due to several reasons. First, the country is large, populous, and comprises several regions with different levels of development. Also, there are more that 6000 hospitals, and a mixed system of public and private healthcare. Finally, there is a complex system of patient transfers among hospitals within regions. In this context, and in order to complement the findings described in previous work, we explore the role of patient movement within and between hospitals on the transmission and incidence of KPC in Brazil. For this, we developed a metapopulation model in which each hospital has two environments (regular ward and ICU facility) and the HCW act as the vectors of pathogen transmission. The connections between hospitals are made using a theoretical Brazilian hospital network based on hospital size and location. The R_0 was calculated in different scenarios defined by the links generated between hospital environments and between hospitals. Numerical simulations were performed to illustrate infection dynamics, and to characterize the sensitivity of R_0 to model parameters such as hospital connectivity, and patient-hospital staff contact rates.

2. Methods

2.1. Hospital network

Due to the lack of information about patient transfers among hospitals, we built a theoretical undirected network using the known location and size (estimated by the number of hospital beds) of Brazilian hospitals. The data was collected between February and April of 2016 via the “National Register of Health-Service Establishments” (Cadastro Nacional de Estabelecimentos de Saúde – CNES) (DATASUS). We excluded hospitals with incomplete data and those with less then ten beds. The resulting network comprises 6214 hospitals classified as general hospital nonspecialized units (only regular wards), or mixed hospitals (both regular wards and ICU facilities). We used the ArcGIS software to geocode hospital locations and to measure the pairwise distance between all hospitals.

We classified the hospitals to four levels: (i) level 1 – hospitals with less than 50 beds; (ii) level 2 – hospitals with 50–199 beds; (ii) level 3 – hospitals with 200–499 beds; and (iv) level 4 – hospitals with more than 499 beds (Ramos et al., 2015). Fig. 1 shows the spatial distribution of the hospitals that make up the network, along with their classification. The hospital network was constructed following the assumption that each hospital is connected to its eight nearest same-/higher-level hospitals. The exception is level 1 hospitals, which are connected only to higher-level hospitals. The result is an undirected, unweighted network,

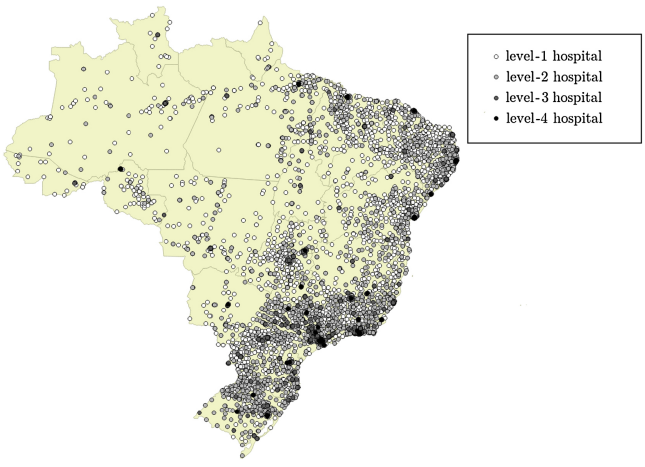

Fig. 1. Geocoding of Brazilian hospitals using ArcGIS. The hospitals are classified in four levels: (i) level 1 – hospitals with less than 50 beds; (ii) level 2 – hospitals with 50–199 beds; (ii) level 3 – hospitals with 200–499 beds; and (iv) level 4 – hospitals with more than 499 beds.

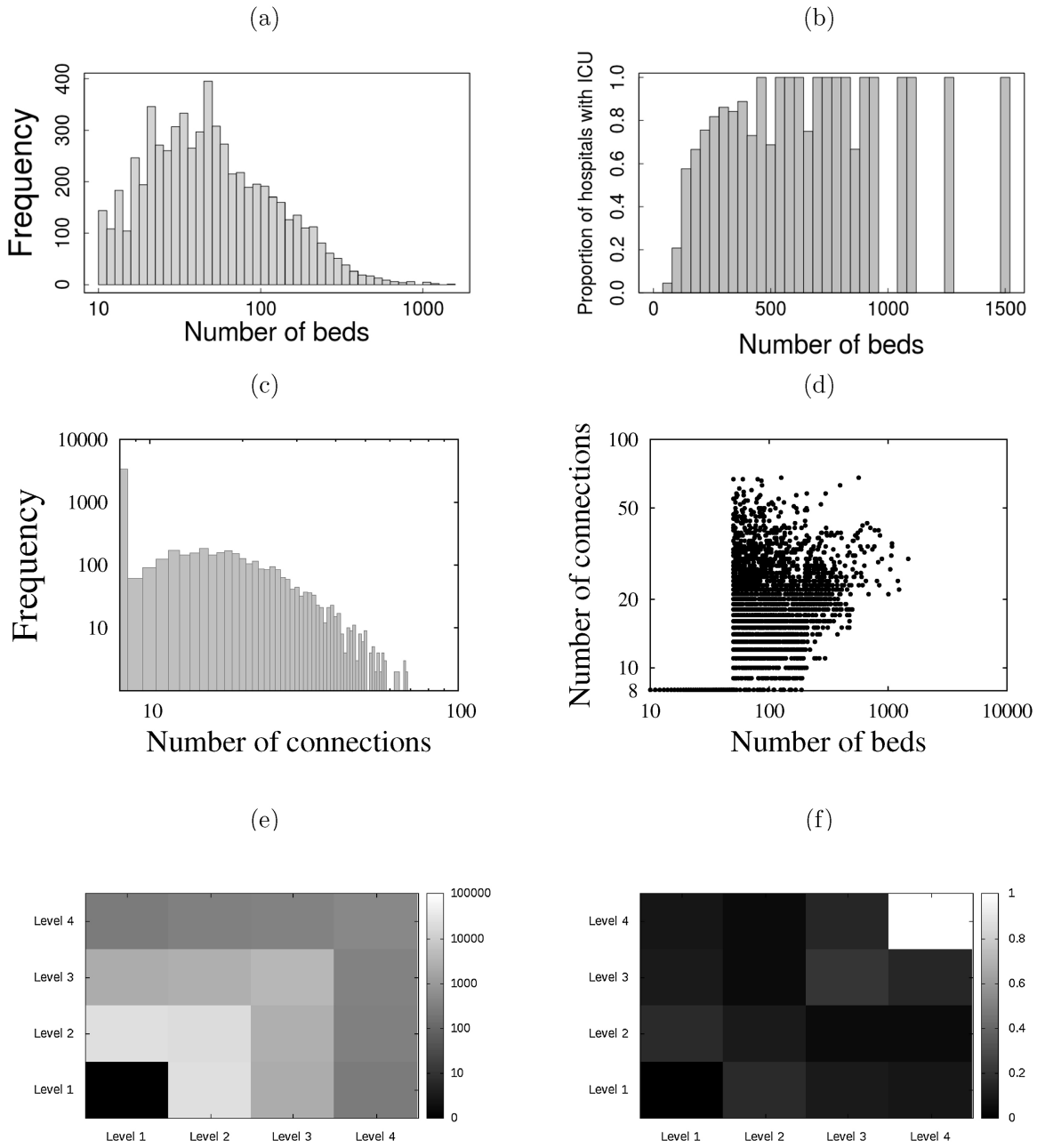

Fig. 2. Network characteristics. (a) Frequency distribution of the number of available beds; (b) The proportion of hospitals having an ICU as a function of the hospital size; (c) Frequency of the network's degree of connectivity; (d) Scatter plot showing the number of connections in the network against the hospital size; (e) Heatmap of the total number of connections between two hospital levels; (f) Heatmap of the average geographic distance between two connected hospitals for different hospital levels.

for which the adjacency matrix is a symmetric matrix with elements 0 or 1. If the element (i, j) of the adjacency matrix is 1, there is a connection between hospitals i and j, meaning patients are transferred between them.

Some characteristics of the topology of the constructed network are shown in Fig. 2. In Fig. 2a, the frequency distribution of the number of available beds is shown; observe that most of the hospitals are level 1 or 2. Fig. 2b shows the proportion of hospitals with ICU service based on their size; in general, hospitals of level 1 or 2 do not have an ICU, and they represent a large amount of Brazilian healthcare facilities. The proportion of hospitals having ICU service increases with hospital size; among hospitals of level 3 and 4 it reaches 85%.

Fig. 2c shows the frequency of degree centrality in the network of hospitals. We see that a large number of hospitals have only eight connections (Fig. 2d), which is not surprising, because by definition all level 1 hospitals have eight connections (being connected to their closest eight level 2+ hospital, yet have no hospitals connecting back to them); the increase in degree centrality depends on hospital size (large-size hospitals are connected with several smaller hospitals), and on the geographic distance between hospitals. Because some regions of Brazil are geographically isolated from others, hospitals of medium size localated in these regions have to be connected with the small ones in

their neighborhood (see Fig. 1).

In Fig. 2e and f, we show the total number of connections and the average geographic distance between hospitals of different levels; the average distance is rescaled by the greatest distance and the results are shown as a heatmap. The highest number of connections occurs among level 1 hospitals and level 2 hospitals; as expected, the number of connections among level 4 hospitals is relatively low when compared to the number of connections among hospitals of level 1 and 2. The distance between two connected level 4 hospitals is highest on average. In summary, low-level hospitals are expected to be connected locally among themselves and with higher-level hospitals, arranged in a local network. Whereas level 4 hospitals are responsible for long-range connections.

2.2. Multi-patch model

We constructed a multi-patch model to simulate the transmission of HAI within and between hospitals. Each patch represents a hospital, and connections between two patches is due to patient transfers. A system of ordinary differential equations (ODEs) captures infection transmission dynamics in each hospital. The variables of the model are healthcare workers (HCW), and patients; and the epidemiological classes are susceptible and colonized individuals. We assume that a hospital can have two distinct environments, differing by the infection-acquiring risk, which are the regular ward and the ICU. Each environment has its own healthcare staff, and again, transmission between these two environments is due to patient movement. The transfer rate between hospitals i and j, $t_{i,j}$, is calculated by multiplying the transfer rate, τ, by the element $m_{i,j}$ of the adjacency matrix that characterizes the hospital network. The Brazilian hospital network comprises two types of hospital: (i) type A – ICU plus regular wards, (ii) type B – only regular wards. Assuming we have n_1 hospitals of type A and n_2 hospitals of type B, then hospitals with ICU occupy the first n_1 columns and rows of the adjacency matrix $M = (m_{ij})$, and the last n_2 columns and rows are occupied by hospitals without ICU (for our system we have $n_1 = 1639$ and $n_2 = 4575$). The ODE system describing infection transmission in hospitals of type A is given by

$$
\begin{aligned}
\dot{U}_{S_i} &= \mu_{U_i} - b_U\beta_U\frac{W^U_{C_i}}{W^U_i}U_{S_i} - \delta_{\mathrm{UP}}U_{S_i} + \delta_{\mathrm{PU}}P_{S_i} - \nu U_{S_i} - \sum_{j=1,j\neq i}^{n_1} t_{j,i}U_{S_i} \\
&+ \sum_{j=1,j\neq i}^{n_1} t_{i,j}U_{S_j},\ \dot{U}_{C_i} = b_U\beta_U\frac{W^U_{C_i}}{W^U_i}U_{S_i} - \delta_{\mathrm{UP}}U_{C_i} + \delta_{\mathrm{PU}}P_{C_i} - \nu U_{C_i} \\
&- \sum_{j=1,j\neq i}^{n_1} t_{j,i}U_{C_i} + \sum_{j=1,j\neq i}^{n_1} t_{i,j}U_{C_j},\ \dot{P}_{S_i} = \mu_{P_i} - b_P\beta_P\frac{W^P_{C_i}}{W^P_i}P_{S_i} + \delta_{\mathrm{UP}}U_{S_i} \\
&- \delta_{\mathrm{PU}}P_{S_i} - \alpha P_{S_i} - \sum_{j=1,j\neq i}^{n_1+n_2} t_{j,i}P_{S_i} + \sum_{j=1,j\neq i}^{n_1} t_{i,j}P_{S_j} + \sum_{j=1}^{n_2} t_{i,j+n_1}E_{S_j},\ \dot{P}_{C_i} \\
&= b_P\beta_P\frac{W^P_{C_i}}{W^P_i}P_{S_i} + \delta_{\mathrm{UP}}U_{C_i} - \delta_{\mathrm{PU}}P_{n_A C_i} - \alpha P_{C_i} - \sum_{j=1,j\neq i}^{n_1+n_2} t_{j,i}P_{C_i} \\
&+ \sum_{j=1,j\neq i}^{n_1} t_{i,j}P_{C_j} + \sum_{j=1}^{n_2} t_{i,j+n_1}E_{C_j},\ \dot{W}^U_{S_i} = \mu_W W^U_i - b_U\beta_W\frac{W^U_{S_i}}{W^U_i}U_{C_i} \\
&+ \lambda W^U_{C_i} - \mu_W W^U_{S_i},\ \dot{W}^U_{C_i} = b_U\beta_W\frac{W^U_{S_i}}{W^U_i}U_{C_i} - \lambda W^U_{C_i} - \mu_W W^U_{C_i},\ \dot{W}^P_{S_i} \\
&= \mu_W W^P_i - b_P\beta_W\frac{W^P_{S_i}}{W^P_i}P_{C_i} + \lambda W^P_{C_i} - \mu_W W^P_{S_i},\ \dot{W}^P_{C_i} \\
&= b_P\beta_W\frac{W^P_{S_i}}{W^P_i}P_{C_i} - \lambda W^P_{C_i} - \mu_W W^P_{C_i},
\end{aligned}
\tag{1}
$$

being $\{i \in \mathbb{N} | 1 \leq i \leq n_1\}$, $W^U_i = W^U_{S_i} + W^U_{C_i}$ and $W^P_i = W^P_{S_i} + W^P_{C_i}$; and in hospitals of type B by

$$
\begin{aligned}
\dot{E}_{S_i} &= \mu_{E_i} - b_P\beta_P\frac{W^E_{C_i}}{W^E_i}E_{S_i} - \alpha E_{S_i} - \sum_{j=1,j\neq n_1+i}^{n_1+n_2} t_{j,n_1+i}E_{S_i} + \sum_{j=1}^{n_1} t_{n_1+i,j}P_{S_j} \\
&+ \sum_{j=1,j\neq i}^{n_2} t_{n_1+i,j+n_1}E_{S_j}, \\
\dot{E}_{C_i} &= b_P\beta_P\frac{W^E_{C_i}}{W^E_i}E_{S_i} - \alpha E_{C_i} - \sum_{j=1,j\neq n_1+i}^{n_1+n_2} t_{j,n_1+i}E_{C_i} + \sum_{j=1}^{n_1} t_{n_1+i,j}P_{C_j} \\
&+ \sum_{j=1,j\neq i}^{n_2} t_{n_1+i,j+n_1}E_{C_j}, \\
\dot{W}^E_{S_i} &= \mu_W W^E_i - b_P\beta_W\frac{W^E_{S_i}}{W^E_i}E_{C_i} + \lambda W^E_{C_i} - \mu_W W^E_{S_i}, \\
\dot{W}^E_{C_i} &= b_P\beta_W\frac{W^E_{S_i}}{W^E_i}E_{C_i} - \lambda W^E_{C_i} - \mu_W W^E_{C_i}.
\end{aligned}
\tag{2}
$$

being $\{i \in \mathbb{N} | 1 \leq i \leq n_2\}$ and $W^E_i = W^E_{S_i} + W^E_{C_i}$.

The model assumptions are: (i) KPC is not endemic in the Brazilian population at large, but is present in hospitals. Consequently, there are no entries of colonized individuals into hospitals; (ii) Patients are moved between the two hospital environments, the ICU and regular wards; (iii) Patients must pass through a regular ward before being discharged from the hospital; (iv) Only ICU patients have a significant mortality rate; (v) Once colonized, a patient remains in this epidemiological state until leaving the hospital; (vi) Transfers among hospitals are given by the Brazilian hospital network; (vii) Workers (hospital staff) can revert from colonized to non-colonized state due to hygiene practices.

Table 1 summarizes the epidemiological classes of the model; model parameters with descriptions and numerical range are given in Table 2.

2.3. Parameter values

Using the Brazilian health ministry website (DATASUS), we computed the number of admissions in the Brazilian healthcare system in the year 2016. This number was divided by 365 and by the total number of available hospital beds in Brazil. We considered that hospitals have a daily patient admission rate proportional to their capacity. Additionally, the number of HCW was estimated using the Brazilian resolution which mandates that, for a healthcare service, one daily physician, one physician on duty, one physiotherapist, one nurse for each 10 beds (or fraction thereof) and one nursery technician for each 2 beds must be present (ANVISA). Healthcare-work shifts operate as eight-hour rotations and we assumed that hand-washing frequency has

Table 1
Compartments of the mathematical model based on the epidemiology of infection transmission. Type A and B hospitals refer to those with and without ICU facility, respectively.

Type	Place	Description	Variable
A	ICU	Number of susceptible patient	U_S
		Number of colonized patient	U_C
		Number of susceptible HCW	W^U_S
		Number of colonized HCW	W^U_C
		Total number of HCW	W^U
A	Ward	Number of susceptible patient	P_S
		Number of colonized patient	P_C
		Number of susceptible HCW	W^P_S
		Number of colonized HCW	W^P_C
		Total number of HCW	W^P
B	Ward	Number of susceptible patient	E_S
		Number of colonized patient	E_C
		Number of susceptible HCW	W^E_S
		Number of colonized HCW	W^E_C
		Total number of HCW	W^E

Table 2
Parameter descriptions with their units and values.

Place	Variable	Description	Unit	Values range	Reference
ICU	μ_U	Patient admission rate	Individuals per day	(0.066, 12.27)	Estimated
	β_U	Transmission probability	–	(0, 1)	–
	ν	Mortality rate	Days^{-1}	(0.005, 0.035)	Ramos et al. (2015), Wunsch et al. (2011)
	δ_{UP}	Transfer rate to ward	Days^{-1}	(0.024, 0.056)	Estimated
	b_U	Number of HCW contacts	Per patient per day	(2, 26)	Jiang et al. (2017)
Ward	μ_P	Patient admission rate	Individuals per day	(0.66, 89.03)	Estimated
	β_P	Transmission probability	–	(0, 1)	–
	α	Patient discharge rate	Days^{-1}	(0.1, 0.2)	Ramos et al. (2015), DATASUS
	δ_{PU}	Transfer rate to ICU	Days^{-1}	(0.04, 0.12)	Estimated
	b_P	Number of HCW contacts	Per patient per day	(2, 26)	Jiang et al. (2017)
Both	μ_W	HCW exit/entry rate	Days^{-1}	3.0	Assumed
	β_W	Transmission probability	–	(0, 1)	Assumed
	λ	Decolonization rate	Days^{-1}	(2, 26)	Assumed

the same range that describes the contact frequency. The rates of transfer between ICU and regular wards were estimated using data from the Medical School of Botucatu (FMB-UNESP) obtained from 2015 to 2016. This data set contains information about patient admission date, movement between ICU and regular wards, and final date (including both discharges and deaths) of 200 patients. A bootstrap method was used to calculate the average time between each patient's movement inside the hospital. Lastly, we calculated the interval for δ_{PU} and δ_{UP} using the inverse of the confidence interval (at 95% of confidence) for these average times. Table 2 gives the model parameter values.

2.4. Scenarios

Three scenarios are explored in order to evaluate the spread of HAIs. The main goal is to identify thresholds for the existence and stability of the disease-free equilibrium (DFE) given by ($\bar{U}_S$, $\bar{P}_S$, $\bar{W}_S^U$, $\bar{W}_S^P$) (hospitals type A) or ($\bar{E}_S$, $\bar{W}_S^E$) (hospitals type B) that characterize HAI-free hospitals.

2.4.1. Scenario I – spreading of a localized infection

Consider the situation where there is no coupling between the ICU and regular wards in a single hospital, i.e., $\delta_{UP} = \delta_{PU=0}$, and no patient is transferred among hospitals, i.e. $\tau = 0$. The index i in Eqs. (1) and (2) can be omitted, and the DFE is given by

$$P_1 = \left(\frac{\mu_U}{\nu}, \frac{\mu_P}{\alpha}, W^U, W^P\right)$$

and the threshold, R_1, can be obtained through the next generation matrix (van den Driessche and Watmough, 2002). In this case,

$$R_1 = \max\{R_{U1}, R_{P1}\}, \tag{3}$$

where

$$R_{U1} = \sqrt{\frac{b_U^2\beta_U\beta_W}{\nu(\lambda+\mu_W)}\frac{\bar{U}_S}{\bar{W}_S^U}} \quad \text{and} \quad R_{P1} = \sqrt{\frac{b_P^2\beta_P\beta_W}{\alpha(\lambda+\mu_W)}\frac{\bar{P}_S}{\bar{W}_S^P}}.$$

If $R_1 < 1$ the infection cannot persist in the hospital. Moreover, if both R_{P1} and R_{U1} are greater than 1 the infection is present in the entire hospital, otherwise if $R_{P1} > 1$ and $R_{U1} < 1$ ($R_{P1} < 1$ and $R_{U1} > 1$) it is present just in the regular ward (ICU) environment. For type B hospitals the threshold is given by

$$R_{E1} = \sqrt{\frac{b_P^2\beta_P\beta_W}{\alpha(\lambda+\mu_W)}\frac{\bar{E}_S}{\bar{W}_S^E}}, \quad \text{with } P_1 = \left(\frac{\mu_E}{\alpha}, W^E\right)$$

therefore, if $R_{E1} > 1$ the infection is present in the regular ward, otherwise if $R_{E1} < 1$ the infection cannot persist in this environment.

2.4.2. Scenario II – individuals are transferring between ICU and regular ward

Consider the transmission dynamics in a single hospital ($\tau = 0$), and $\delta_{PU} \neq 0$ and $\delta_{UP} \neq 0$. This case takes into account the movement of patients between ICU and regular wards. The DFE is given by

$$P_2 = \left(\frac{\mu_U(\alpha+\delta_{\mathrm{PU}}) + \mu_P\delta_{\mathrm{PU}}}{\nu(\alpha+\delta_{\mathrm{PU}}) + \alpha\delta_{\mathrm{UP}}}, \frac{\mu_P + \delta_{\mathrm{UP}}\bar{U}_S}{\alpha+\delta_{\mathrm{PU}}}, W^U, W^P\right),$$

for which

$$R_2 = \frac{(R_{U2}+R_{P2}) + \sqrt{(R_{U2}+R_{P2})^2 - 4R_{U2}R_{P2}\left(1 - \frac{\delta_{\mathrm{UP}}\delta_{\mathrm{PU}}}{(\nu+\delta_{\mathrm{UP}})(\alpha+\delta_{\mathrm{PU}})}\right)}}{2} \tag{4}$$

with

$$R_{U2} = \frac{b_U^2\beta_U\beta_W}{(\lambda+\mu_W)\left(\nu+\delta_{\mathrm{UP}}\left(1-\frac{\delta_{\mathrm{PU}}}{\alpha+\delta_{\mathrm{PU}}}\right)\right)}\frac{\bar{U}_S}{\bar{W}_S^U},$$

and

$$R_{P2} = \frac{b_P^2\beta_P\beta_W}{(\lambda+\mu_W)\left(\alpha+\delta_{\mathrm{PU}}\left(1-\frac{\delta_{\mathrm{UP}}}{\nu+\delta_{\mathrm{UP}}}\right)\right)}\frac{\bar{P}_S}{\bar{W}_S^P}.$$

If $R_2 > 1$ the infection persists in the hospital, otherwise it dies out. In contrast to scenario I, the disease is either present in both hospital environments or completely absent. Note that $\delta_{UP}\delta_{PU} \to 0 \Rightarrow R_2 \sim \max\{R_{U2}, R_{P2}\}$. This limit can be achieved making $\delta_{UP} = 0$ or $\delta_{PU} = 0$, which means that no patient is transferred from the ICU to a regular ward or from a regular ward to the ICU. When both parameters are zero, the environments are isolated and we recover the result obtained in scenario I. On the other hand, when $\delta_{UP} \to \infty$ and $\delta_{PU} \to \infty \Rightarrow R_2 \sim R_{U2} + R_{P2}$. In this case, intra-hospital transfer rates are so high that we cannot distinguish between the two environments.

2.4.3. Scenario III – coupling among hospitals

In this more extended system, it is convenient to use a vectorial notation to expedite an explicit expression for the epidemic threshold (Bowong et al., 2013). In bold we have P and U (E) as vectors with dimension n_1 (n_2), and *diag* (**X**) represents a diagonal matrix composed of the elements of **X**. Thus

$$\dot{\mathbf{U}}_\mathbf{S} = \boldsymbol{\mu}_U - b_U\beta_U \text{diag}(\mathbf{W}^\mathbf{U})^{-1}\text{diag}(\mathbf{W}^\mathbf{U}_\mathbf{C})\mathbf{U}_\mathbf{S} - (\delta_{\text{UP}} + \nu)\mathbf{U}_\mathbf{S} + \delta_{\text{PU}}\mathbf{P}_\mathbf{S} + T_U\mathbf{U}_\mathbf{S},$$
$$\dot{\mathbf{U}}_\mathbf{C} = b_U\beta_U \text{diag}(\mathbf{W}^\mathbf{U})^{-1}\text{diag}(\mathbf{W}^\mathbf{U}_\mathbf{C})\mathbf{U}_\mathbf{S} - (\delta_{\text{UP}} + \nu)\mathbf{U}_\mathbf{C} + \delta_{\text{PU}}\mathbf{P}_\mathbf{C} + T_U\mathbf{U}_\mathbf{C},$$
$$\dot{\mathbf{P}}_\mathbf{S} = \boldsymbol{\mu}_P - b_P\beta_P \text{diag}(\mathbf{W}^\mathbf{P})^{-1}\text{diag}(\mathbf{W}^\mathbf{P}_\mathbf{C})\mathbf{P}_\mathbf{S} + \delta_{\text{UP}}\mathbf{U}_\mathbf{S} - (\delta_{\text{PU}} + \alpha)\mathbf{P}_\mathbf{S} + T_P\mathbf{P}_\mathbf{S} + T_{\text{EP}}\mathbf{E}_\mathbf{S},$$
$$\dot{\mathbf{P}}_\mathbf{C} = b_P\beta_P \text{diag}(\mathbf{W}^\mathbf{P})^{-1}\text{diag}(\mathbf{W}^\mathbf{P}_\mathbf{C})\mathbf{P}_S + \delta_{\text{UP}}\mathbf{U}_\mathbf{C} - (\delta_{\text{PU}} + \alpha)\mathbf{P}_\mathbf{C} + T_P\mathbf{P}_\mathbf{C} + T_{\text{EP}}\mathbf{E}_\mathbf{C},$$
$$\dot{\mathbf{E}}_\mathbf{S} = \boldsymbol{\mu}_E - b_P\beta_P \text{diag}(\mathbf{W}^\mathbf{E})^{-1}\text{diag}(\mathbf{W}^\mathbf{E}_\mathbf{C})\mathbf{E}_\mathbf{S} - \alpha\mathbf{E}_\mathbf{S} + T_E\mathbf{E}_\mathbf{S} + T_{\text{PE}}\mathbf{P}_\mathbf{S},$$
$$\dot{\mathbf{E}}_\mathbf{C} = b_P\beta_P \text{diag}(\mathbf{W}^\mathbf{E})^{-1}\text{diag}(\mathbf{W}^\mathbf{E}_\mathbf{C})\mathbf{E}_\mathbf{S} - \alpha\mathbf{E}_\mathbf{C} + T_E\mathbf{E}_\mathbf{C} + T_{\text{PE}}\mathbf{P}_\mathbf{C},$$
$$\dot{\mathbf{W}}^\mathbf{U}_\mathbf{C} = b_U\beta_W \text{diag}(\mathbf{W}^\mathbf{U})^{-1}\text{diag}(\mathbf{W}^\mathbf{U}_\mathbf{S})\mathbf{U}_\mathbf{C} - (\lambda + \mu_W)\mathbf{W}^\mathbf{U}_\mathbf{C},$$
$$\dot{\mathbf{W}}^\mathbf{P}_\mathbf{C} = b_P\beta_W \text{diag}(\mathbf{W}^\mathbf{P})^{-1}\text{diag}(\mathbf{W}^\mathbf{P}_\mathbf{S})\mathbf{P}_\mathbf{C} - (\lambda + \mu_W)\mathbf{W}^\mathbf{P}_\mathbf{C}$$
$$\dot{\mathbf{W}}^\mathbf{E}_\mathbf{C} = b_P\beta_W \text{diag}(\mathbf{W}^\mathbf{E})^{-1}\text{diag}(\mathbf{W}^\mathbf{E}_\mathbf{S})\mathbf{E}_\mathbf{C} - (\lambda + \mu_W)\mathbf{W}^\mathbf{E}_\mathbf{C}$$

where T_U, T_P, T_E, T_{PE} and T_{EP} are computed using the adjacency matrix that characterize the Brazilian hospital network, such that:

(i) T_U is a $n_1 \times n_1$ dimension matrix with $t^u_{i,j}$ given by

$$t^u_{i,j} = \begin{cases} t_{i,j} & \text{if } i \neq j, \\ -\sum_{k=1,k\neq i}^{n_1} t_{k,i} & \text{if } i = j. \end{cases}$$

(ii) T_P is a $n_1 \times n_1$ dimension matrix with $t^p_{i,j}$ given by

$$t^p_{i,j} = \begin{cases} t_{i,j} & \text{if } i \neq j, \\ -\sum_{k=1,k\neq i}^{n_1+n_2} t_{k,i} & \text{if } i = j. \end{cases}$$

(iii) T_E is a $n_2 \times n_2$ dimension matrix with $t^e_{i,j}$ given by

$$t^e_{i,j} = \begin{cases} t_{i+n_1,j+n_1} & \text{if } i \neq j, \\ -\sum_{k=1,k\neq i}^{n_1+n_2} t_{k,i+n_1} & \text{if } i = j. \end{cases}$$

(iv) T_{EP} is a $n_1 \times n_2$ dimension matrix where $t^{\text{ep}}_{i,j} = t_{i,j+n_1}$.
(v) T_{PE} is the transpose of T_{EP}.

The DFE is given by

$$P_3 = (\tilde{\mathbf{U}}_\mathbf{S}, \tilde{\mathbf{P}}_\mathbf{S}, \tilde{\mathbf{E}}_\mathbf{S}, \mathbf{W}^\mathbf{U}_\mathbf{S}, \mathbf{W}^\mathbf{P}_\mathbf{S}, \mathbf{W}^\mathbf{E}_\mathbf{S}),$$

where

$$\tilde{\mathbf{U}}_\mathbf{S} = (\text{diag}(\nu + \delta_{\text{UP}}) - T_U)^{-1}(\boldsymbol{\mu}_U + \text{diag}(\delta_{\text{PU}})\tilde{\mathbf{P}}_\mathbf{S}), \quad \tilde{\mathbf{E}}_\mathbf{S} = (\text{diag}(\alpha_2) - T_E)^{-1}(\boldsymbol{\mu}_E + T_{\text{PE}}\tilde{\mathbf{P}}_\mathbf{S}),$$

and

$$\tilde{\mathbf{P}}_\mathbf{S} = [(\text{diag}(\alpha_1 + \delta_{\text{PU}}) - T_P) - \text{diag}(\delta_{\text{UP}})(\text{diag}(\nu + \delta_{\text{UP}}) - T_U)^{-1}\text{diag}(\delta_{\text{PU}}) - T_{\text{EP}}(\text{diag}(\alpha_2) - T_E)^{-1}T_{\text{PE}}]^{-1} \times [\boldsymbol{\mu}_P + \text{diag}(\delta_{\text{UP}})(\text{diag}(\nu + \delta_{\text{UP}}) - T_U)^{-1}\boldsymbol{\mu}_U + T_{\text{EP}}(\text{diag}(\alpha_2) + T_E)^{-1}].$$

Using the next generation operator we have

$$F = \begin{bmatrix} 0_{2n_1+n_2\times 2n_1+n_2} & F_1 \\ F_2 & 0_{2n_1+n_2\times 2n_1+n_2} \end{bmatrix}, \quad \text{and} \quad V^{-1} = \begin{bmatrix} A^{-1} & 0_{2n_1+n_2\times 2n_1+n_2} \\ 0_{2n_1+n_2\times 2n_1+n_2} & B^{-1} \end{bmatrix}$$

with

$$F_1 = \begin{bmatrix} b_U\beta_U \text{diag}(\mathbf{W}^\mathbf{U})^{-1}\text{diag}(\mathbf{U}_\mathbf{S}) & 0_{n_1\times n_1} & 0_{n_1\times n_2} \\ 0_{n_1\times n_1} & b_P\beta_P \text{diag}(\mathbf{W}^\mathbf{P})^{-1}\text{diag}(\mathbf{P}_\mathbf{S}) & 0_{n_1\times n_2} \\ 0_{n_2\times n_1} & 0_{n_2\times n_1} & b_P\beta_P \text{diag}(\mathbf{W}^\mathbf{E})^{-1}\text{diag}(\mathbf{E}_\mathbf{S}) \end{bmatrix},$$

$$F_2 = \begin{bmatrix} \text{diag}(b_U\beta_W) & 0_{n_1\times n_1} & 0_{n_1\times n_2} \\ 0_{n_1\times n_1} & \text{diag}(b_P\beta_W) & 0_{n_1\times n_2} \\ 0_{n_2\times n_1} & 0_{n_2\times n_1} & \text{diag}(b_P\beta_W) \end{bmatrix},$$

$$A = \begin{bmatrix} 0_{n_1\times n_2} & -\text{diag}(\delta_{\text{PU}}) & 0_{n_1\times n_2} \\ -\text{diag}(\delta_{\text{UP}}) & \text{diag}(\alpha_1 + \delta_{\text{PU}}) - T_P & -T_{\text{EP}} \\ 0_{n_2\times n_1} & -T_{\text{PE}} & \text{diag}(\alpha_2) + T_E \end{bmatrix}$$

and

$$B^{-1} = \begin{bmatrix} \text{diag}(\lambda + \mu_W)^{-1} & 0_{n\times n} \\ 0_{n\times n} & \text{diag}(\lambda + \mu_W)^{-1} \end{bmatrix}.$$

The threshold R_3 is given by the spectral radius of FV^{-1},

$$R_3 = \rho(F_1B^{-1}F_2A^{-1}). \tag{5}$$

Therefore, if $R_3 > 1$ infection transmission persists in the hospital, otherwise it stops.

2.5. Sensitivity analysis

The sensitivity analysis measures how variation in input parameters affects the model output. Among the several existing techniques, we used the Partial Rank Correlation Coefficient (PRCC), which is a sampling-based method and works well for nonlinear, but monotonic, relationships (Marino et al., 2008; Cariboni et al., 2007). To establish the importance of patient movement in a single hospital (δ_{PU} and δ_{UP}) and patient transfer between hospitals (τ) we performed a SA using as output the threshold values R_2 and R_3 given by Eqs. (4) and (5), respectively. For scenario II, the sensitivity analysis includes the steady state, P_2, and the thresholds for disease persistence in each environment, R_{U2} and R_{P2}.

The parameters were sampled using a Latin Hypercube Sampling (LHS) scheme, a Monte-Carlo technique that generates a sample of size N by dividing the whole parameter space into N intervals that are each sampled once (Cariboni et al., 2007; Marino et al., 2008). Because we had no prior information on the distribution of parameters, we selected uniform distributions bounded by plausible ranges. Table 2 lists the parameter ranges used in the analysis. We used a sample of size $N = 1000$.

3. Results

Fig. 3 shows the temporal evolution of the number of colonized patients when a local infection is set up (scenario I). Starting from the arrival of one infected individual in each sector (ICU and regular ward), four long-term scenarios for HAI transmission, represented by different parameter sets, are highlighted. In (a), (b), (c), and (d) we have, respectively, infection transmission sustained in the entire hospital, infection transmission restricted to only the ICU environment, infection transmission restricted to only the regular wards, and the disease free equilibrium. Although the values of R_1 are the same in panel (b) and (c), the transmission dynamics and the steady states are different, with infection prevalence higher in the ICU.

Fig. 4 shows the temporal evolution of the number of colonized patients when there is coupling between ICU and regular wards through patient movement (scenario II). Two distinct situations, given by

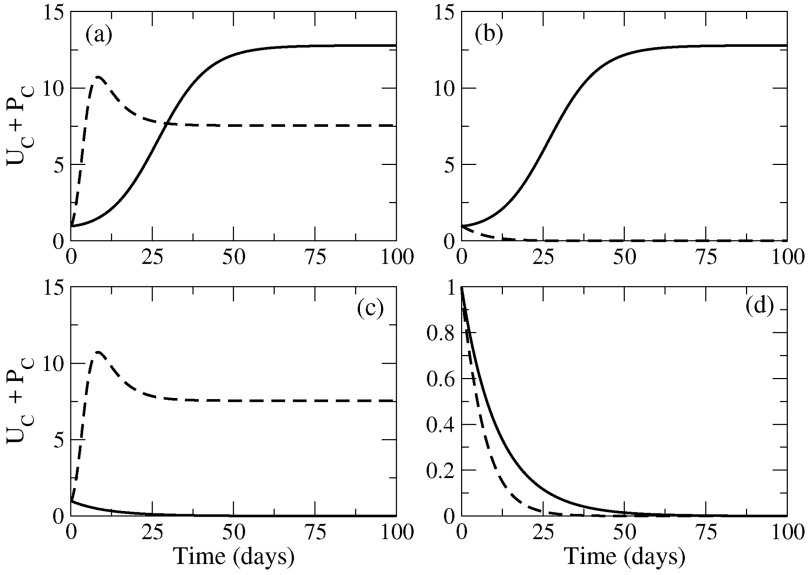

Fig. 3. Number of colonized individuals versus time for different parameters sets. The continuous line shows the disease transmission at ICU services and the dashed line at wards. In (a) we have $R_{U1} = 2.576$ and $R_{P1} = 2.576$ ($R_1 = 2.576$), in (b) $R_{U1} = 2.576$ and $R_{P1} = 0.164$ ($R_1 = 2.576$), (c) $R_{U1} = 0.164$ and $R_{P1} = 2.576$ ($R_1 = 2.576$), and in (d) $R_{U1} = 0.164$ and $R_{P1} = 0.164$ ($R_1 = 0.164$).

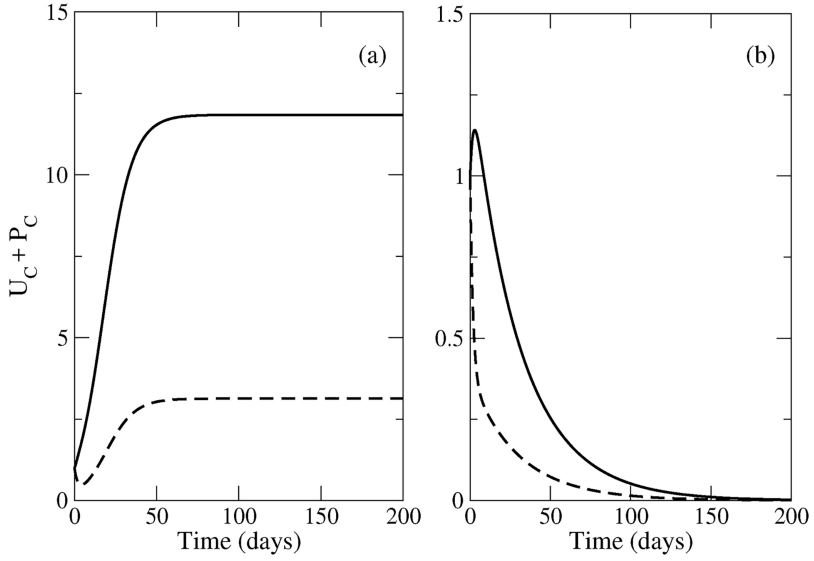

Fig. 4. Number of colonized individuals versus time for different parameters sets. The continuous line shows the disease transmission at ICU services and the dashed line at wards. In (a) we have $R_{U2} = 1.976$, $R_{P2} = 0.083$ ($R_2 = 2.0076$), in (b) $R_{U2} = 0.164$, $R_{P2} = 0.164$ ($R_2 = 0.711$).

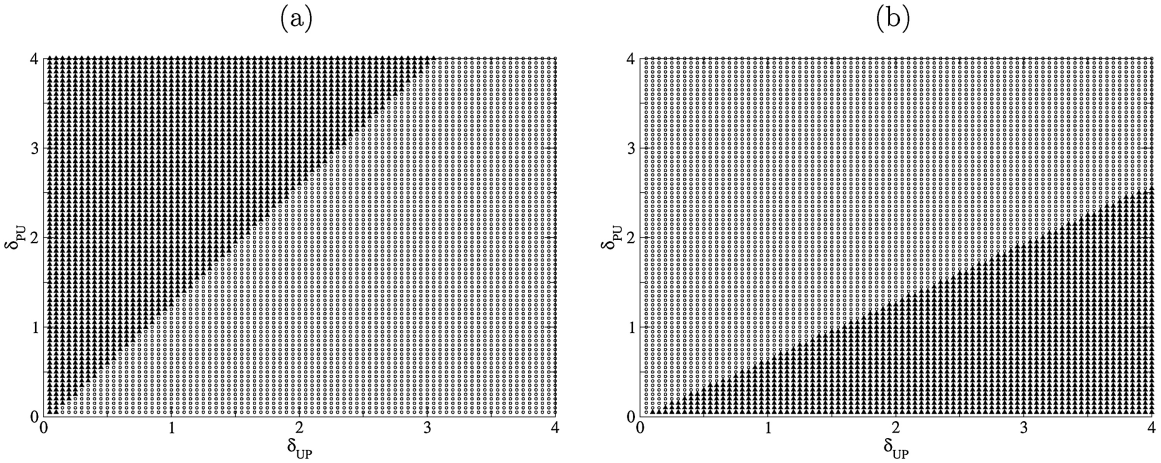

Fig. 5. Parameter space showing the role of the connection between ICU and ward services in an hospital and disease (infection) prevalence. The symbols identify the regions of disease persistence (▲) and disease extinction (∘). In (a) we have $b_U = 5$ and $b_P = 3$ and in (b) we have $b_U = 2$ and $b_P = 7$ The others parameters are $\beta_W = 0.2$, $\lambda = 0.1$, $\mu_U = 2.2$, $\mu_P = 2.6$, $\nu = 0.099$, $\alpha = 0.2$, $\mu_W = 3$ and $\beta_U = \beta_P = 0.3$.

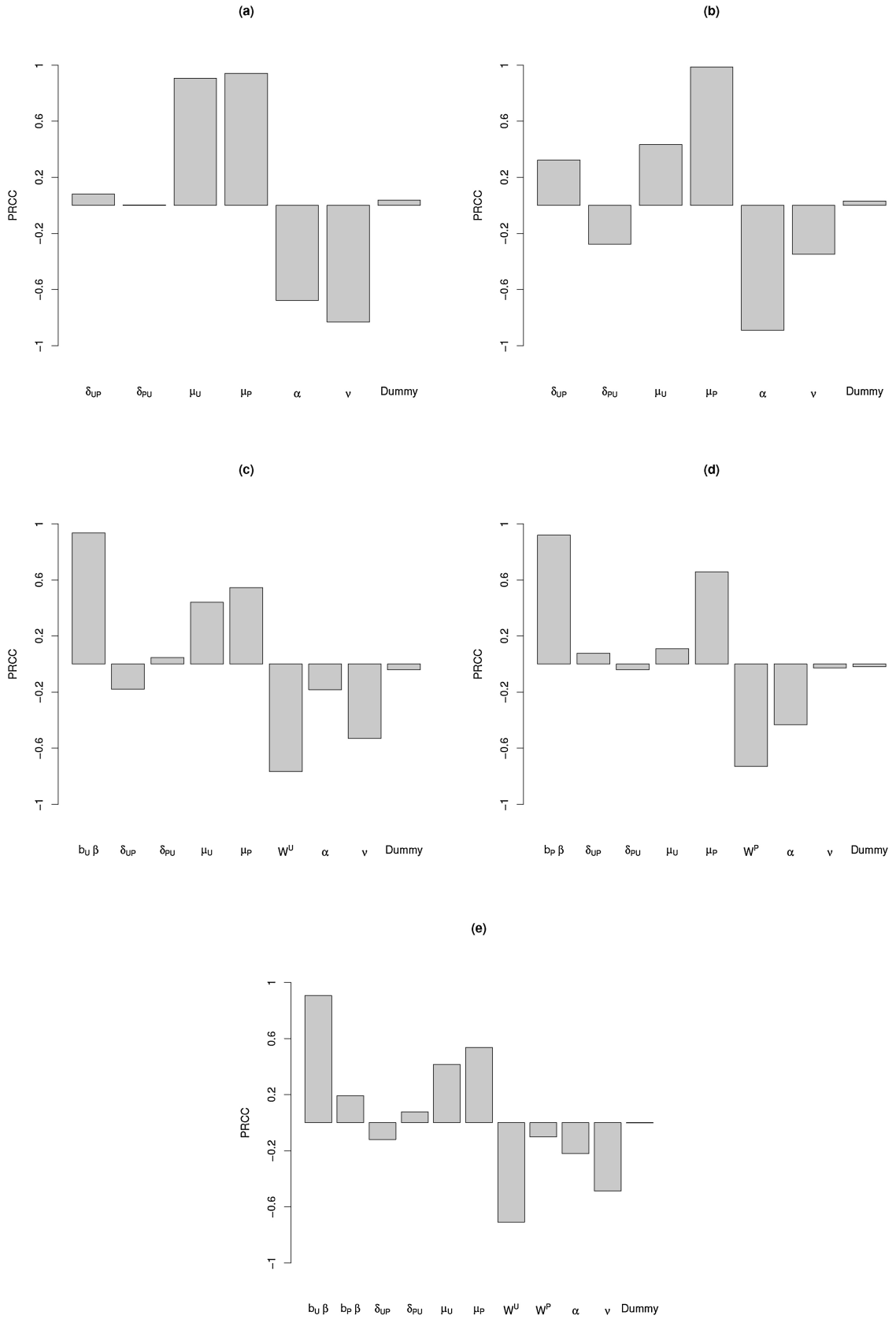

Fig. 6. PRCC results for scenario II. The outputs are: (a) $\bar{U}_S$, (b) $\bar{P}_S$, (c) R_{U2}, (d) R_{P2} and (e) R_2. A negative-control "dummy" parameter was used to assign a zero value for a sensitivity index. Therefore, when the PRCC of a sensitivity index is less than the PRCC of the dummy parameter we can say that the influence of this input parameter on the measured output is not relevant. We set up $b_U\beta_U$, $bP\beta P$, $bU\beta W$, $bP\beta W$ in the range of [0, 26], $W^P \in [9, 1215]$, and $W^U \in [5, 169]$.

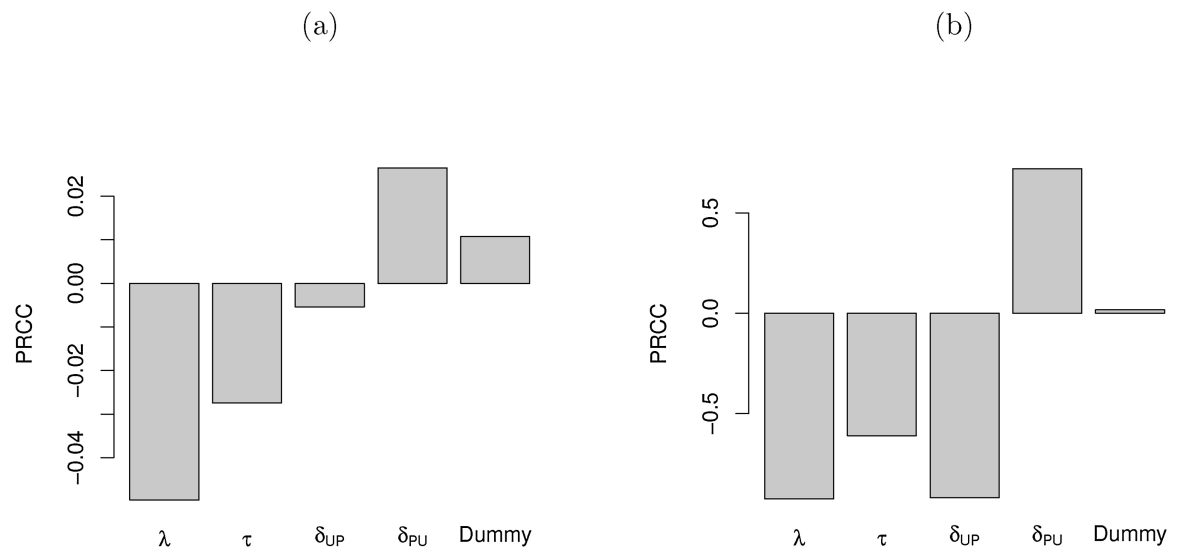

Fig. 7. PRCC results for scenario III. The output is R_3. A negative-control "dummy" parameter was used to assign a zero value for a sensitivity index. Therefore, when the PRCC of a sensitivity index is less than the PRCC of the dummy parameter we can say that the influence of this input parameter on the measured output is not relevant. In (a) $\beta_U = \beta_{P=}\beta W = \beta = 0.001$ and $bU = bP = b = 14\,\text{day}^{-1}$, and in (b) $\beta U = \beta P = \beta W = \beta = 0.1$ and $bU = bP = b = 14\,\text{day}^{-1}$.

different parameter sets, summarize all possibilities from infection transmission throughout the hospital to a hospital free of HAI transmission. In this scenario, infection transmission is possible in a more complex scenario that involves coupling between ICU and regular wards. In order to explore the role of the linkage between the two hospital environments, we kept fixed all parameter values except δ_{UP} and δ_{PU}. Fig. 5 shows in the parameter space $\delta_{PU} \times \delta_{UP}$ the regions of stability of the steady states. We see that for the same set of parameters (in this case (δPU, δUP)) we can have disease (infection) free equilibrium or infection spreading. Overall, in panel (a) disease persistence is not observed when δUP increases, and when δPU increases it depends strongly on δUP values. On the other hand, in panel (b) the increase of δPU promotes disease extinction. These two situations highlight the importance of hospital environments in disease prevalence. The parameters were chosen in such way that in panel (a) the infection transmission is relatively augmented in the ICU and in panel (b) it is relatively augmented in the regular ward.

Fig. 6 shows the PRCC analysis for scenario II. We see that ν and α, respectively the mortality rate in ICU and the discharge rate from the regular ward, always contribute to decreases in $\bar{U}_S$, $\bar{P}_S$ and R_2. An increase in the number of HCW W^U (W^P) has a positive effect on transmission control R_2, lowering the level of infection R_{U2} (R_{P2}). An increase in either the infection probability or the contact rate between patients and HCW leads to an increase in R_{U2} and R_{P2}. An increase in the rate of patient admissions promotes the increase of R_2. Overall the transmission rates and the parameters pertaining to the ICU environment are most influential for transmission and persistence of the infection.

The last scenario is explored through a sensitivity analysis and the concept of "source-sink" dynamics, which assumes that transmission in some environments cannot be sustained ("sink") without the arrival of new infected individuals to re-establish a chain of transmission ("source"). Each hospital was defined as "source" or "sink" based on its R_0 (threshold) value, which measure its ability to maintain transmission alone; a "source" hospital has $R_0 > 1$ and a "sink" hospital has $R_0 < 1$ (Gravel et al., 2010).

From the sensitivity analysis, the importance of $b_U\beta$ and $b_P\beta$ on the output R_3 was very high and rendered an evaluation of the contribution of the other parameters practically impossible. Therefore, we set $b_U = b_P = 14\ \text{day}^{-1}$, and $\beta_U = \beta_P = \beta W = \beta = 0.001$ (or $\beta = 0.1$) and performed the analysis again. We also fixed the total number of HCW according to the size of the hospital (ANVISA). For $\beta = 0.001$, the order of importance is λ, τ, and δPU; the parameter δUP was assigned as unimportant (see Fig. 7 in panel (a)). However, when β was increased to 0.1, δUP was assigned as important, even more so than τ (see Fig. 7 in panel (b)). The emerging hypothesis is that the amount of sources (or sinks) in the system changes the order of importance of the parameters. To test this, Figs. 8 and 9 show the distribution of $R0$ values of the hospitals that comprise the network; $R0 = R1$ (Eq. (3)) for hospitals without ICU, and $R0 = R2$ (Eq. (4)) for hospitals with ICU. For the set of parameters used in the simulations, when $\beta = 0.001$ all hospitals had $R0 < 1$ which characterizes all of them as sinks. In contrast, when $\beta = 0.1$, only a fraction of hospitals without ICU have $R0 < 1$ and all hospitals with ICU have $R0 > 1$. An interesting feature is that the coupling between the hospitals, given by the parameter τ, may decrease or increase the $R3$ value of the network, when compared with the individual values obtained for each hospital in the network. For the case where $\beta = 0.001$, $R0 \in [0.004, 0.169]$ and for the entire network the mean value is $\bar{R}_3 = 0.005\,[0.003, 0.016]$, and for the case when $\beta = 0.1$, $R0 \in [0.314, 15.321]$ and for the entire network the mean value is $\bar{R}_3 = 37.861\,[18.539, 140.996]$

4. Discussion

The proposed model describes HAI transmission in a Brazilian healthcare network that was constructed taking into account hospital sizes (given by the number of available beds) and distance between hospitals. The model assumptions capture the dynamics of KPC transmission and the hospital routine procedures in Brazil. The model was parametrized using data from the Brazilian health ministry website and from the hospital of FMB-UNESP. While the network used is plausible, it is important to recognize that the connections in the network are derived from general principles, and are therefore not equivalent to the true representation of the Brazilian hospital network, and may not have the same properties as the real world network. Consequently, the model is best used to understand broad principles of transmission within and between hospital environments, and specific policies involving real hospitals would better be derived from more detailed data, which is not readily available.

In order to study the transmission dynamics, both within and between hospitals, we explored three scenarios that differ by patient movement between hospital environments and patient transfer among hospitals. In all cases, thresholds for infection transmission were obtained and control measurements were explored.

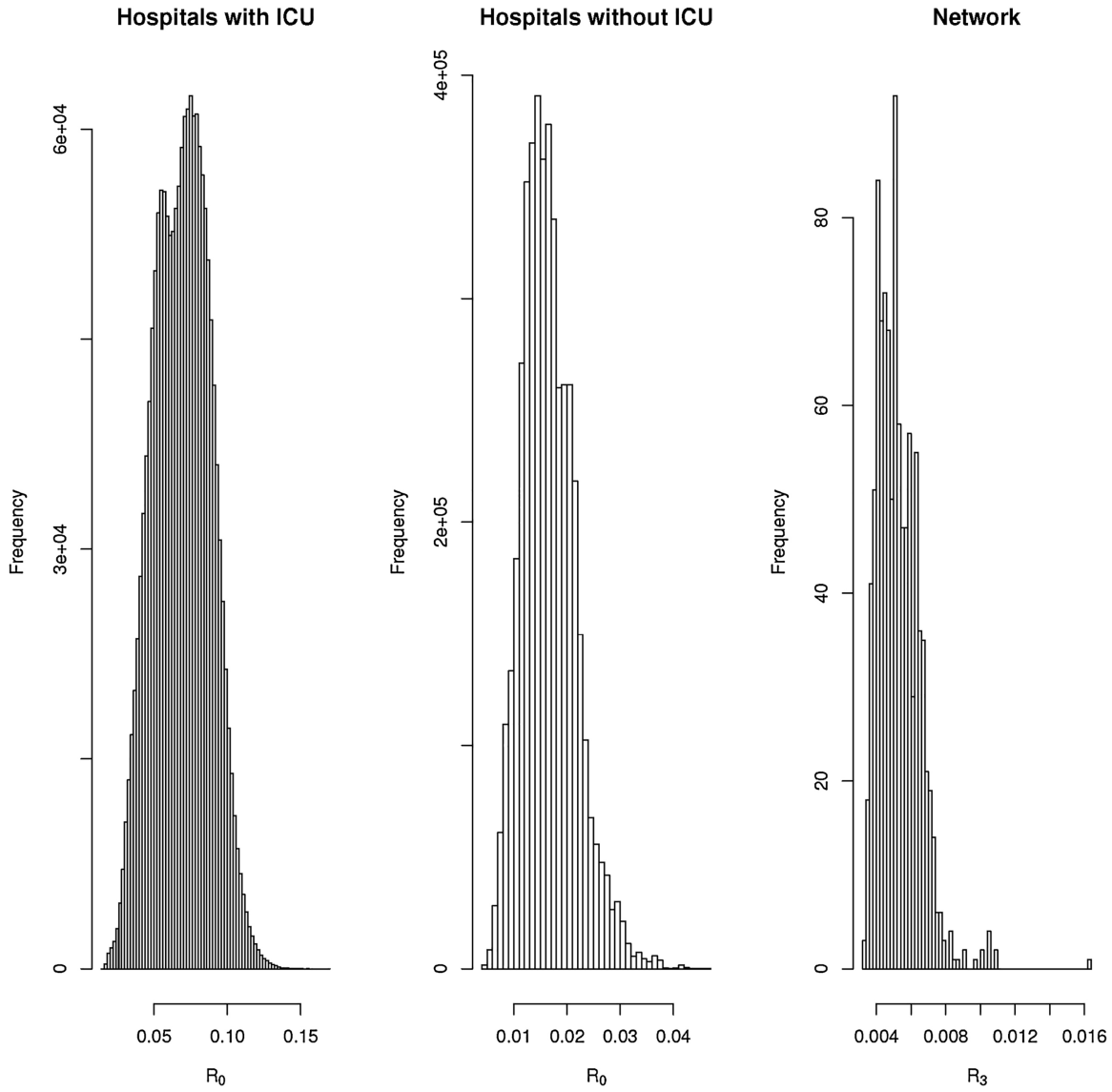

Fig. 8. Histogram of R_0 value for each hospital in the network using the set of parameters of Fig. 7(a). Hospitals without ICU service have $R_0 = R_1$ (Eq. (3)), and the ones with ICU service have $R_0 = R_2$ (Eq. (4)). The R_0 of the entire network is given by R_3 which mean value is 0.005.

In the first scenario, there were no linkages between ICU and regular wards, nor were there any patient transfers between hospitals. In this case the threshold value for transmission (R_1) is given by the maximum of R_{U1} and R_{P1}, which respectively describe the infection transmission thresholds in ICU and regular wards. Both thresholds have similar expressions to those derived from mathematical models of vector-borne diseases, except that the ratio between the two populations (host and vector) is reversed when compared to classical vector-borne disease models (Keeling and Rohani, 2008). This happens because of the assumption that each patient requires a fixed number of contacts per day; therefore, increasing the number of HCW, the number of contacts that each HCW will perform decreases, which reduces infection transmission between patients and HCW. Moreover, it implies that for HAI transmission, increasing HCW (vectors for transmission) decreases R_1 (Barnes et al., 2010). Concordantly, literature points out that decreased staffing (understaffing) is one of the major drivers of transmission of multidrug-resistant bacteria in hospitals (Daud-Gallotti et al., 2012; Clements et al., 2008). In summary, if $R_1 < 1$ the infection cannot persist in a hospital, whereas if both R_{P1} and R_{U1} exceed 1 the infection is present in the entire hospital. Otherwise if $R_{P1} > 1$ and $R_{U1} < 1$ ($R_{P1} < 1$ and $R_{U1} > 1$) infection is present in only the regular ward (ICU) environment. R_1 measures the control effort to stop infection transmission; it depends on model assumptions, biological parameters that characterize the infectious agent, and hospital features such as hospital size and the ratio between the number of patients and the number of staff.

The second scenario considered hospitals with linkage between ICU and regular wards, and the resulting threshold R_2 is strongly dependent on the transfer rates between these two environments (δ_{PU} and δ_{UP}). In this case, infection either spreads in the whole hospital ($R_2 > 1$) or dies out ($R_2 < 1$). Moreover, the effect of patient transfer on infection dynamics is non-trivial, including the phenomenon whereby increasing the transfer rates can promote extinction or persistence of infection (Fig. 5). Again, the expressions for R_{U2} and R_{P2} suggest a strong dependence of R_2 on the number of HCW. The sensitivity analysis summarizes the importance of each parameter on transmission, with $b_U\beta_{U,}$ $_WU$, μ_P and ν, respectively representing the infection transmission rate, the total number of healthcare workers at the ICU, the patient admission rate and the patient mortality rate, emerging as the most important parameters in this scenario (Fig. 6e). Comparing the regular ward and the ICU environment, this study shows that the ICU environment is the main target for control of infection transmission.

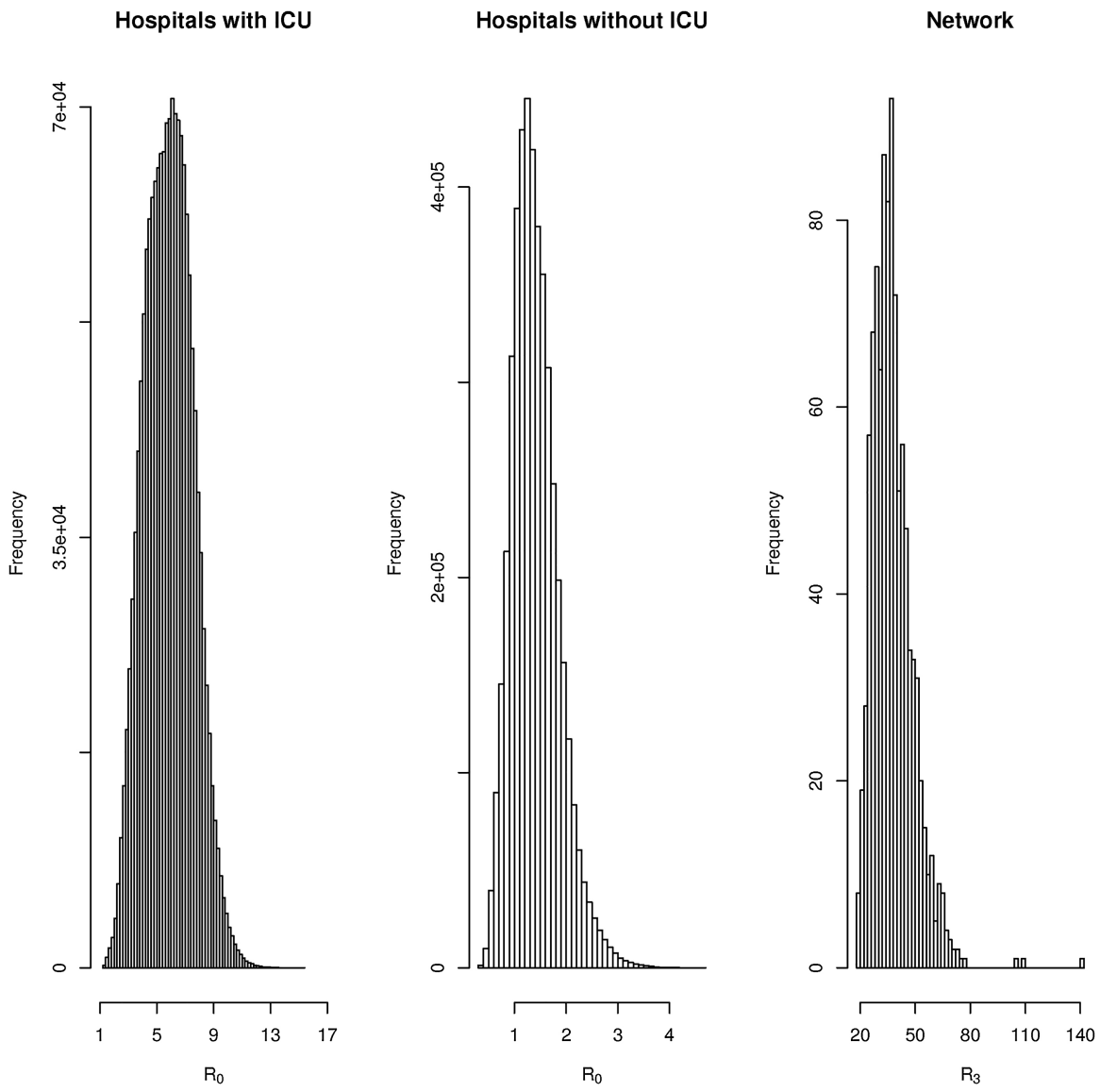

Fig. 9. Histogram of R_0 value for each hospital in the network using the set of parameters of Fig. 7(b). Hospitals without ICU service have $R_0 = R_1$ (Eq. (3)), and the ones with ICU service have $R_0 = R_2$ (Eq. (4)). The R_0 of the entire network is given by R_3 which mean value is 37.861.

In the third scenario, where we considered the entire network of Brazilian hospitals, the impact of model input parameters on the threshold R_3 was analysed through a sensitivity analysis technique. We found that when β increases (transmission probability), the parameter δ_{UP} (transfer rate to ward) becomes important and negatively influences R_3, because disease prevalence is higher in the ICU sector compared to regular wards. Given that the number of HCW in each hospital is fixed, the most important parameter for control was a hygiene measure given by the parameter λ (decolonization rate). Hospitals with ICU facilities are the ones with a higher proportion of infection sources and a higher $R_0\,(=R_2)$ value. The PRCC analysis demonstrated that the transfer rate among hospitals (τ) tended to decrease R_3. This is likely because most hospitals in the network (4575/6214) have only regular wards, which have a lower $R_0\,(=R_1)$ value. Surprisingly, for a fixed value of τ, the coupling among hospitals can both decrease or increase the $R_0\,(=R_3)$ of the network, when compared with the individual values ($R_0 \in \{R_1, R_2\}$) obtained for each hospital in the network (Figs. 8 and 9) reinforcing our hypothesis that the network of hospitals reflect a sink-source model for infection transmission. In this context, the referral and counter-referral system is a good strategy to reduce infection prevalence. According to such a system, a patient arriving at a healthcare service is "referenced" (forwarded) to a unit of greater complexity in order to receive the care they need. On treatment completion, the patient must be "counter-referred", that is, the professional staff send the patient back to the unit of origin so that continuity of service is upheld.

Spatial variation in hospital sizes, presence or absence of an ICU, degree of connectivity, and inter-hospital transfer rate are ingredients that may promote source-sink dynamics at a regional and national scale. The reintroduction of the infectious agent may re-establish local transmission; the existence of clustered sinks may result in lower infection persistence, though this would require explicit testing that goes beyond the scope of this manuscript. However, understanding the factors that augment or diminish the strength of these interactions has the potential to guide effective decisions and actions. The manipulation of the topology of the network can be used to address optimal control strategies to halt transmission among hospitals, similar to methods that target individuals in a network (Salath and Jones, 2010), or isolate districts embedded in a network to limit spatial spread of infection (Kramer et al., 2016).

The network explored here has some specific features related to the complexity of a big and non-homogeneous country, with several levels of population density, economic activities, and human development

index. We observe a large number of small hospitals without an ICU, and a small number of large hospitals, most of them with ICU service. Hospitals of level 1 and 2 are expected to be highly clustered, while hospitals of level 4 have large geographic distance among them and are responsible for long-range connections. These network results are expected to reflect the reality. However, due to the lack of data we are unable, for now, to confirm them.

Novel multidrug resistant organisms will continue to emerge and spread worldwide. The case for KPC in Brazil is an example of rapid dissemination of a resistance phenotype among healthcare networks. By understanding these dynamics, it may be possible to slow or even control the spread of those pathogens within a country as complex as Brazil. No hospital is an island. Therefore, the control of antimicrobial resistance may require extensive country-level interventions which include rules for patient transfer between hospitals and/or other healthcare facilities.

5. Conclusions

Overall, our results suggest that a relatively high number of HCW per patient, along with healthcare compliance with hygiene are the key parameters to control the dissemination of HAIs. Furthermore, identifying the hospitals in the network that act as sources of infection, and determining the location inside a hospital where the incidence of infection is high can help to optimize control efforts. In this case, patient movement between wards in a hospital or between hospitals should be evaluated based on HAI prevalence, underscoring the importance of a local and national active surveillance system. Although our study was based on data from one hospital in Brazil and on a theoretical network of hospitals, the model can be parametrized with pathogens other than KPC-producing enterobacteria, and comparisons between hospitals and hospital networks will help to establish the robustness of our results more broadly.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

CPF and CMCB proposed the main idea of the work. MFB and HMG collected the data, provide the parameters values and the important literature. TNV made the code, generated the results and figures. CPF and AWP wrote the first version of the manuscript. All the authors contributed on the process of write and discuss of the manuscript.

Declaration of interest

None.

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