

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

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Hospital-acquired infections (HAI) are mainly caused by opportunistic bacteria resistant to antibiotics. Ninety percent of HAIs occur in Intensive Care Units (severity of illness of patients, the extensive use of wide-spectrum antibiotics and invasive procedures).

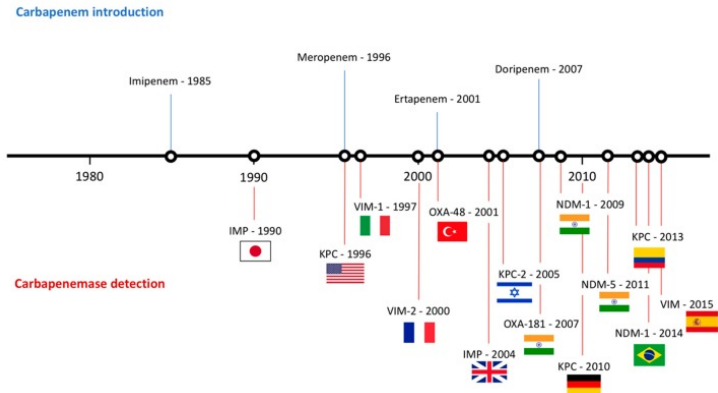
These infections increase patient morbidity and mortality, and impose healthcare costs.

Transmission occurs at the level of single hospital, and at regional, and national level by interhospital patient transfers.

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%.

Carbapenem-resistant Enterobacteriaceae (CRE)

Timeline representing the introduction of carbapenems and the appearance of carbapenemases worldwide (from Antibiotics (Basel). 2019 Sep; 8(3): 122).



The resistance gene spreads both clonally and by horizontal gene transfer.
P.S. KPC in Brazil (Antimicrob Agents Chemother. 2009 53(1):333-34).

Objective

Focusing on the role of patient movement within and between hospitals on the transmission and incidence of enterobacteria producing the *Klebsiella pneumoniae* Carbapenemase (KPC), 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 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).

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.

Hospitals can be classified as a source or a sink of infection based on its R_0 value. Can the concept of *source-sink* dynamics be used to define strategies of control?

Hospital network (2011)

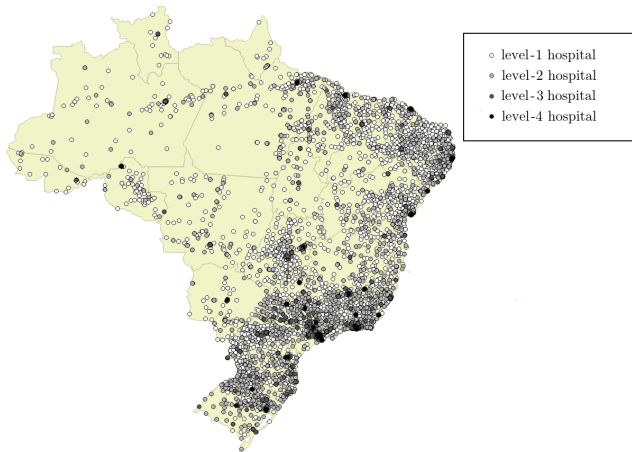
Due to the lack of information about patient transfers among hospitals, we built a theoretical **undirected, unweighted network using the known location and size** (estimated by the number of hospital beds) of Brazilian hospitals. We used the ArcGIS software to geocode hospital locations and to measure the pairwise distance between all hospitals.

We excluded hospitals with incomplete data and those with less than ten beds.

Each hospital is connected to its eight nearest same-/higher-level hospitals (level 1 hospitals are connected only to higher-level hospitals).

The resulting network comprises 6214 hospitals classified as general hospital nonspecialized units (only regular wards, total of 4575), or mixed hospitals (both regular wards and ICU facilities, total of 1639).

Geocoding of Brazilian hospitals



(i) level 1 - less than 50 beds; (ii) level 2 - 50 to 199 beds; (iii) level 3 - 200 to 499 beds; and (iv) level 4 - more than 499 beds.

Multi-patch model (2002)

Each patch represents a hospital, and connections between two patches is due to patient transfers.

We assume that a hospital can have two distinct environments, differing by the infection-acquiring risk, which are the regular ward and the ICU facility, and the healthcare workers (HCW) act as the vectors of pathogen transmission.

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.

ODE system

Variables are healthcare workers, and patients; both susceptible or colonized

$$\left\{ \begin{array}{l} \dot{U}_i = \mu_{U_i} - b_U \beta_U \frac{W_{C_i}^U}{W_i^U} U_{S_i} - \delta_{UP} U_{S_i} + \delta_{PU} P_{S_i} - \nu U_{S_i} - \sum_{j \neq i} \tau_{j,i} U_{S_i} + \sum_{j \neq i} \tau_{i,j} U_{S_j} \\ \dot{U}_{C_i} = b_U \beta_U \frac{W_{C_i}^U}{W_i^U} U_{S_i} - \delta_{UP} U_{C_i} + \delta_{PU} P_{C_i} - \nu U_{C_i} - \sum_{j \neq i} \tau_{j,i} U_{C_i} + \sum_{j \neq i} \tau_{i,j} U_{C_j}, \\ \dot{P}_i = \mu_{P_i} - b_P \beta_P \frac{W_{C_i}^P}{W_i^P} P_{S_i} + \delta_{UP} U_{S_i} - \delta_{PU} P_{S_i} - \alpha P_{S_i} - \sum_{j \neq i} \tau_{j,i} P_{S_i} + \sum_{j \neq i} \tau_{i,j} P_{S_j} \\ \dot{P}_{C_i} = b_P \beta_P \frac{W_{C_i}^P}{W_i^P} P_{S_i} + \delta_{UP} U_{C_i} - \delta_{PU} P_{C_i} - \alpha P_{C_i} - \sum_{j \neq i} \tau_{j,i} P_{C_i} + \sum_{j \neq i} \tau_{i,j} P_{C_j} \end{array} \right.$$

$$HCW \left\{ \begin{array}{l} \dot{W}_{S_i}^K = \mu_W W_i^K - b_K \beta_W \frac{W_{S_i}^K}{W_i^K} K_{C_i} + \lambda W_{C_i}^K - \mu_W W_{S_i}^K, \\ \dot{W}_{C_i}^K = b_K \beta_W \frac{W_{S_i}^K}{W_i^K} K_{C_i} - \lambda W_{C_i}^K - \mu_W W_{C_i}^K. \end{array} \right.$$

Each environment has its own healthcare staff; $K = \{U, P\}$; $W_i^K = W_{S_i}^K + W_{C_i}^K$.

Parameter estimation

Using the [Brazilian health ministry website](#), 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](#).

The number of HCW was estimated using the [Brazilian resolution](#). Healthcare-work shifts operate as [eight-hour rotations](#) and we assumed that [hand-washing frequency](#) has 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.

Scenario I - Spreading of a localized infection

No coupling between the ICU and regular wards in a single hospital, and no patient is transferred among hospitals. The DFE is given by

$$P_1 = (\bar{U}_S, 0, \bar{P}_S, 0, \bar{W}_S^U, 0, \bar{W}_S^P, 0) = \left(\frac{\mu_U}{\nu}, 0, \frac{\mu_P}{\alpha}, 0, W^U, 0, W^P, 0 \right)$$

and the threshold, R_1 , can be obtained through the next generation matrix. Therefore,

$$R_1 = \max\{R_{U1}, R_{P1}\}, \quad (1)$$

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.

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.

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 .**

The literature points out that decreased staffing (understaffing) is one of the major drivers of transmission of multidrug-resistant bacteria in hospitals.

Scenario II - Individuals are transferring between ICU and regular ward

Consider the **transmission dynamics in a single hospital**. The DFE is given by

$$P_2 = \left(\frac{\mu_U(\alpha + \delta_{PU}) + \mu_P\delta_{PU}}{\nu(\alpha + \delta_{PU}) + \alpha\delta_{UP}}, 0, \frac{\mu_P + \delta_{UP}\bar{U}_S}{\alpha + \delta_{PU}}, 0, W^U, 0, W^P, 0 \right),$$

for which

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

with

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

and

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

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 $\delta_{UP}\delta_{PU} \rightarrow 0 \implies R_2 \sim \max\{R_{U2}, R_{P2}\}$. When both parameters are zero, the environments are isolated and we recover the result obtained in scenario I.

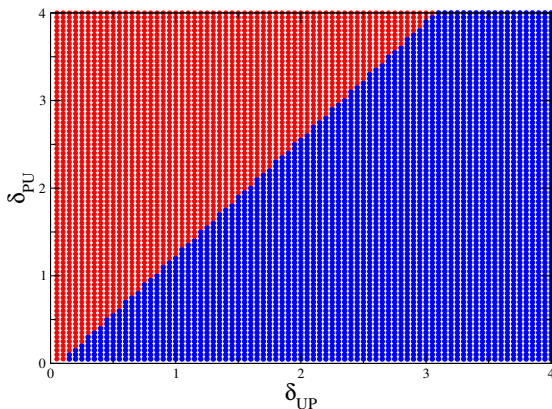
On the other hand, when $\delta_{UP} \rightarrow \infty$ and $\delta_{PU} \rightarrow \infty \implies R_2 \sim R_{U2} + R_{P2}$. In this case, intra-hospital transfer rates are so high that we cannot distinguish between the two environments.

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.

Overall the transmission rates and the parameters pertaining to the ICU environment are most influential for transmission and persistence of the infection; with $b_U\beta_U$, W^U , μ_P and ν emerging as the most important parameters in this scenario.

Parameter space $\delta_{PU} \times \delta_{UP}$

Disease persistence (in red) is not observed when δ_{UP} increases, and when δ_{PU} increases it depends strongly on δ_{UP} values. The parameters were chosen in such way that in panel the infection transmission is relatively augmented in the ICU.



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.

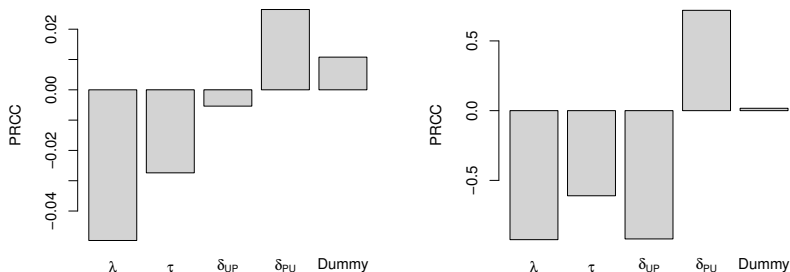
Using the next generation operator, an explicit equation for R_3 that be obtained; R_3 is calculated numerically. If $R_3 > 1$ infection transmission persists in the hospital, otherwise it stops.

This 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 $R_0 < 1$.

Sensitivity analysis, R_3 (control of the infection)

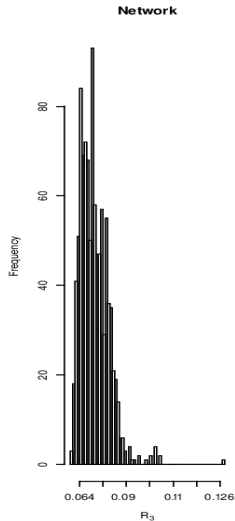
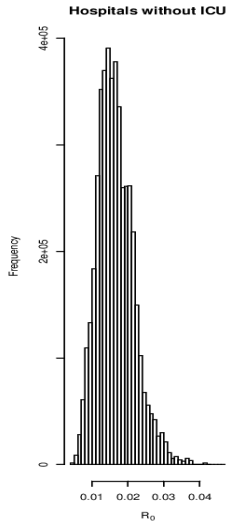
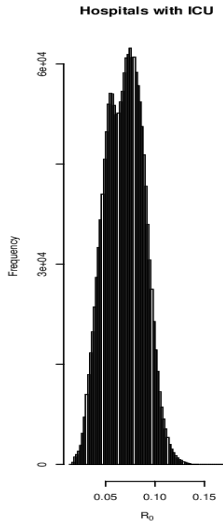
For $\beta = 0.001$, the order of importance is λ , τ , and δ_{PU} ; the parameter δ_{UP} was assigned as unimportant (left). However, when β was increased to 0.1, δ_{UP} was assigned as important, even more so than τ (right). **The hypothesis is that the amount of sources (or sinks) in the system changes the order of importance of the parameters.**



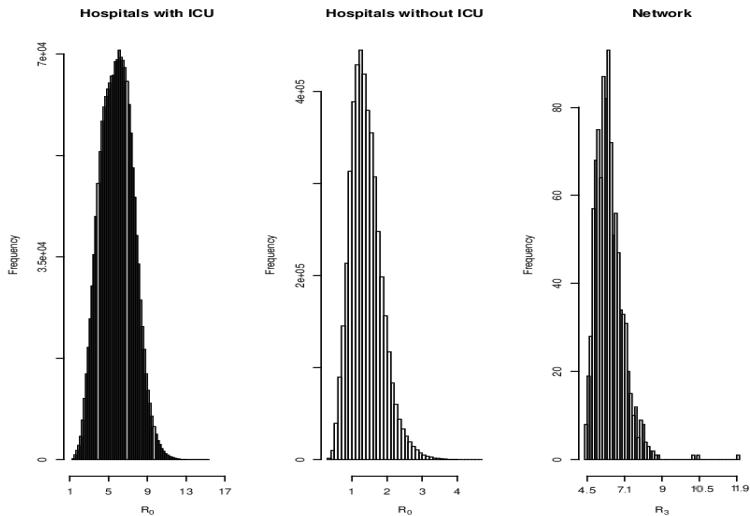
P.S. $b_U\beta_U = b_P\beta_P = b_U\beta_W = b_P\beta_W$.

Histogram of R_0 value

When $\beta = 0.001$ all hospitals have $R_0 < 1$ which characterizes all of them as sinks.



When $\beta = 0.1$, only a fraction of hospitals without ICU have $R_0 < 1$ and all hospitals with ICU have $R_0 > 1$.



Summarizing

For the case where $\beta = 0.001$, $R_0 = 0.031$ [0.004, 0.169] and for the entire network the mean value is $\bar{R}_3 = 0.072$ [0.058, 0.128], and for the case when $\beta = 0.1$, $R_0 = 2.578$ [0.314, 15.321] and for the entire network the mean value is $\bar{R}_3 = 6.093$ [4.306, 11.874].

When β increases, the parameter δ_{UP} becomes important and negatively influences R_3 , because disease prevalence is higher in the ICU sector compared to regular wards.

The coupling between the hospitals, given by the parameter τ , may decrease or increase the R_3 value of the network, when compared with the individual values obtained for each hospital in the network.

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 .

In the case of Brazil, the transfer rate among hospitals tended to decrease R_3 . This is likely because most hospitals in the network (4575/6214) have only regular wards (referral and counter-referral system).

Conclusion

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.

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 context, the referral and counter-referral system is a good strategy to reduce infection prevalence.

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.

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.

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.

The manipulation of the topology of the network can be used to address optimal control strategies to halt transmission among hospitals.

What about the source-sink dynamics? Can the knowledge of it helping to design efficiently control strategies?

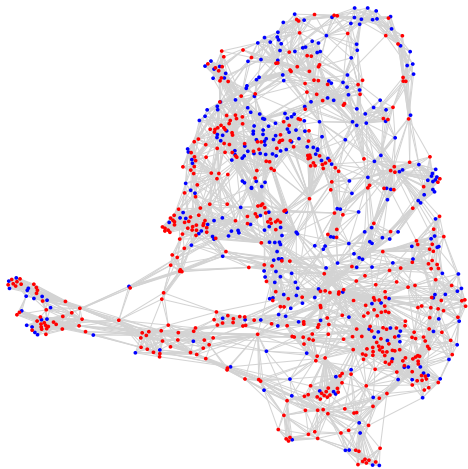
São Paulo state: source and sink hospitals

The network comprises 859 hospitals, classified as source (red) and sink (blue).

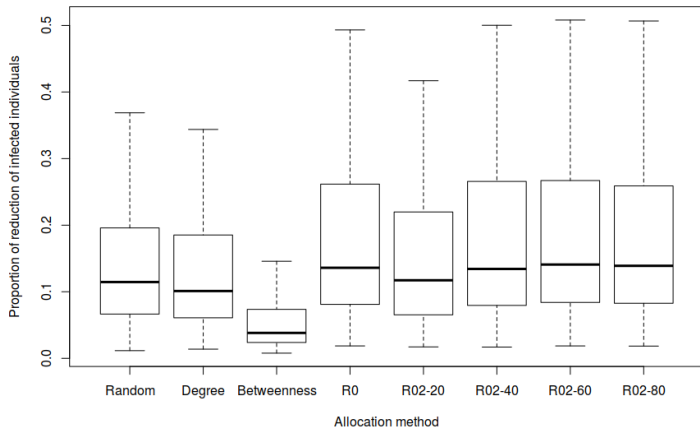
Allocation of control units:

- (1) randomly,
- (2) degree-centrality (# of links incident upon a node),
- (3) betweenness-centrality (# of times a node acts as a bridge along the shortest path between two other nodes),
- (4) R_0 value.

Each unit of control diminished 25% of the transmission, and reduction is cumulative.



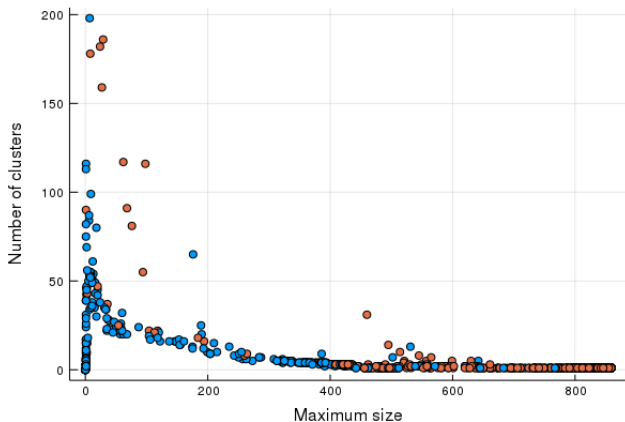
Control effort: distribution of 500 units of control



Different allocations of infection control resources lead to differences in control efficacy \implies target control: source-type hospitals.

Cluster Investigation Analysis

network community structure.. source clusters.



1. Vilches, TN *et al.* (2018) The role of intra and inter-hospital patient transfer in the dissemination of healthcare-associated multidrug-resistant pathogens. *Epidemics*, DOI 10.1016/j.epidem.2018.11.001
2. Donker, T *et al.* (2012). Hospital networks and the dispersal of hospital-acquired pathogens by patient transfer. *PLoS ONE*, DOI 10.1371/journal.pone.0035002
3. Karkada, UH *et al.* (2011) Limiting the spread of highly resistant hospital-acquired microorganisms via critical care transfers: a simulation study. *Intensive Care Med*, DOI 10.1007/s00134-011-2341-y

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