Received: Added at production | Revised: Added at production | Accepted: Added at production

DOI: xxx/xxxx

RESEARCH ARTICLE

Analysis of Network Interventions with an Application to Hospital Acquired Infections

Daniel K. Sewell* for the CDC MInD-Healthcare Program

[1]Department of Biostatistics, University of Iowa, IA, USA

Correspondence
*Daniel K. Sewell, 145 N. Riverside Dr., Iowa City, IA, 52242 USA. Email: daniel-sewell@uiowa.edu

Abstract

Regional interventions to prevent the spread of hospital acquired infections, vaccination campaigns, and information dissemination strategies are examples of treatment interventions applied to members of a network with the intent of effecting a network-wide change. In designing clinical trials or determining policy changes, it may not be cost effective or otherwise possible to treat all actors of a network. There is a notable lack of study designs and statistical frameworks with which to plan a network-wide intervention in this context and analyze the resulting data. This paper builds off of the network autocorrelation model in order to provide such a framework for a pre-post study design. We derive key quantitative measures of the network-wide treatment effect, exact formulas for power analyses of these measures, and extensions for the context in which the network is unknown. As the treatment assignation is part of the network-wide treatment, we provide methods for determining the assignation which optimizes the overall treatment effect over all members of the network subject to any arbitrary set of implementation costs and cost constraint. We implement these methods on *Clostridium difficile* data for the state of California, where the hospitals are linked through patient sharing.

KEYWORDS:
Infectious disease; Network autocorrelation model; Optimization; Power analyses; Study design

1 | INTRODUCTION

Experimental units are often intricately linked in complex ways. In such contexts, treatments applied to some experimental units will invariably influence the outcomes of others e.g.,[1], and hence the network describing these connections cannot simply be ignored when comparing treatment arms. Two contexts (at least) occur in which studies involving networked subjects take place. In the first, the goal is to find a treatment effect by comparing those individuals treated vs. a set of controls, in which case the network is a nuisance to be dealt with. In the second, the goal is to evaluate the effect of treating all or a targeted subset of the network members on the outcomes of *all* members of the network, both treated and untreated. In this latter context the network, rather than imposing nuisance parameters, is to be leveraged in order to augment the treatment effect.

There is a quickly growing body of research to address this first case, focusing on estimating treatment effects on individuals while accounting for what is termed spillover effects. Spillover effects occur when one wishes to determine what effect, if any, a treatment has on an individual, but due to the experimental units being networked, the controls' outcomes are affected by the outcomes of those treated. This is a violation of the no-interference assumption required for standard statistical procedures[2,3].

Examples of the occurrence of a spillover effect include the use of online networks to diffuse health behaviors[4], and medical treatments for helminths in children[5]. With a few exceptions, much of the work focuses on finding a hierarchical structure to the network in which various components are disconnected, i.e., there exist groups of network members which may interfere with other members of the same group but not members of other groups e.g.,[6,7,8].

While the above work focuses on estimating the effect of an individual level treatment based on a randomized trial, this paper focuses on the second case in which the thing of interest is not so much an individual level change as a change to all members of the network. Vaccination strategies are an extreme example of this in which the individual treatment effect is often already known, but various partial assignation strategies may lead to differences in the vulnerability of the entire network to a disease e.g.,[9]. The primary motivation for this work is the effort to reduce hospital-acquired infections (HAIs) or the spread of multidrug resistant organisms through the healthcare system. The EUREGIO MRSA-net[10] is an example of this endeavor, where researchers employed a "search and follow" strategy across 40 hospitals along the Germany-Netherlands border in order to reduce meticillin-resistant *Staphylococcus aureus* (MRSA). These hospitals were interconnected via patient sharing, and the exhaustive screening of incoming patients demonstrated that these inter-hospital connections were an important pathway of disease diffusion.

Although all network members in the EUREGIO MRSA-net study underwent the same intervention, in general it may be expected that applying a treatment to all health care facilities within a region during a clinical trial would be cost prohibitive and arguably unnecessary to demonstrate the effectiveness of a regional intervention. Similarly, in vaccine campaigns there may be a limited supply of vaccines that requires a targeted treatment assignation procedure. In both cases the goal is to minimize costs while maximizing the desired effect across the network. Indeed, unlike the first case described above, the treatment assignation may itself be part of the treatment, thus ruling out any inference based on the randomization distribution dictated by the experimental design.

This paper aims at providing guidance on designing and analyzing the results of a study investigating the effect of treating a subset of an entire network. Specifically, this paper makes the following contributions. First, we describe a general framework in which to analyze a network intervention study. Within this framework we identify key quantities of interest in the study with clinical meaningfulness and provide closed form power calculations. Second, we provide a method for finding the optimal treatment assignation subject to any arbitrary set of network member-specific costs associated with implementing the proposed treatment. The method is optimal in the sense of making the largest network-wide change due to the treatment assignation.

The outline of the remainder of the paper is as follows. Section 2 provides a review of the network autocorrelation model which is core to our proposed approach. Section 3 provides the basis for an analytical framework for a network intervention study, providing the statistical model, a method for computing power, and a solution for the optimal treatment assignation. Section 4 provides a simulation study illustrating the optimality of our treatment assignation procedure. Section 5 describes the context of designing a network intervention study on California hospitals with the aim of reducing the statewide number of *Clostridium difficile* cases. Section 6 provides a brief conclusion.

2 | A BRIEF REVIEW OF NETWORK AUTOCORRELATION MODELS

2.1 | Notation and context

Before proceeding, we first wish to provide some notation and contextual information. Suppose we have n actors, or network members, and the response variable measured on these n actors is denoted by the $n \times 1$ vector $\boldsymbol{y}$. We have p covariates (including in most cases an intercept) captured in the $n \times p$ matrix X. The network amongst the actors can be represented by an adjacency matrix A, where A_{ij} equals the (possibly weighted and/or directed) edge between i and j. For example, in the application outlined in Section 5, A_{ij} corresponds to the number of patients transferred to hospital i from hospital j. Note that we do not assume that A is symmetric, although in many instances this will be true.

2.2 | Network autocorrelation models

Network autocorrelation models (NAMs) are very often the model of choice when studying the contamination effects over a network on a response variable of interest, as well as accounting for such contamination effects in the investigation of the relationship of other covariates with the response. Indeed,[11] describes the NAM as the "workhorse" for capturing network effects on the network members' attributes. While there are variants of the NAM, we will focus here on the network effects model[12]

given by

$$\boldsymbol{y} = X\boldsymbol{\beta} + \rho A\boldsymbol{y} + \boldsymbol{\epsilon}, \tag{1}$$

where $\boldsymbol{\beta}$ is the typical vector of regression coefficients, ρ is the network autocorrelation parameter, and $\boldsymbol{\epsilon}$ is typically assumed to follow a multivariate normal distribution with mean $\mathbf{0}$ and covariance matrix $\sigma^2 I_n$. Hence each actor is a function of both actor-specific characteristics and the response of that actor's neighbors in the network.

There are three primary approaches to estimation of the NAM: maximum likelihood (ML) estimators, instrumental variables (IV), and Bayesian approaches. ML estimation has a long history[13], and while ML is in general appealing to statisticians it is known that these estimators have finite sample bias (e.g.,[14]). [15] provides a cogent argument via a simulation study that Bayesian estimators ought to be preferred over ML estimation. A critical work by[16], extended or modified in many other works (e.g., [17,18]), derived consistent and asymptotically normal parameter estimates using an IV approach. Their approach relaxes the assumption that the errors $\boldsymbol{\epsilon}$ are normally distributed and is dramatically less computationally expensive than the ML approach for large networks.

[19] provided a powerful extension of the work by[16], which we will denote as KP07. Developed with the purpose of addressing heteroscedastic errors, consistent and asymptotically normal estimators were provided under the relaxed assumptions that the errors had mean $\mathbf{0}$ and arbitrary covariance matrix Σ. The NAM under these relaxed assumptions will be the basis for the proposed network intervention study design. While we recommend the readers to look at their original work for technical details and regularity conditions[†], below we provide the closed form estimators. First, let $\boldsymbol{\gamma} := (\boldsymbol{\beta}', \rho)'$, and let $Z = (X, A\boldsymbol{y})$. Then a consistent estimator of $\boldsymbol{\gamma}$ is

$$\hat{\boldsymbol{\gamma}} = (\widehat{Z}'\widehat{Z})^{-1}\widehat{Z}\boldsymbol{y}, \text{ where } \widehat{Z} := H(H'H)^{-1}H'Z, \text{ and } H := (X, AX, A^2X, \ldots, A^qX) \tag{2}$$

The matrix H is used to instrument Z through least squares estimate of $\mathbb{E}(Z) = (X, A\mathbb{E}(\boldsymbol{y}))$. The justification of the structure of H follows from the Neumann series representation of the mean of $\boldsymbol{y}$:

$$\begin{aligned}\mathbb{E}(\boldsymbol{y}) &= (I - \rho A)^{-1}X\boldsymbol{\beta} \\ &= \sum_{k=0}^{\infty} \rho^k A^k X\boldsymbol{\beta}\end{aligned}$$

for $|\rho| < 1$. Hence H ought to be composed of the linearly independent columns of $(X, AX, A^2X, \ldots, A^qX)$, the span of which should approximately include the ideal instrument $\mathbb{E}(Z)$. Note that in practice it is suggested that q, a user-defined positive integer, is usually one or two[16].

To obtain the asymptotic covariance matrix of $\hat{\boldsymbol{\gamma}}$, we first denote the matrix $\Psi := n^{-1}H'\Sigma H$, where again $\Sigma := \mathrm{Cov}(\boldsymbol{\epsilon})$. A consistent estimator $\widehat{\Psi}$ of Ψ is given element-wise by

$$\widehat{\Psi}_{rs} = \frac{1}{n}\sum_{i=1}^{n}\sum_{j=1}^{n} H_{ir}H_{js}\hat{\boldsymbol{\epsilon}}_i\hat{\boldsymbol{\epsilon}}_j K(d_{ij}/d), \tag{3}$$

where d_{ij} is some measure of distance between actors i and j, d is some threshold value, and $K(\cdot)$ is a kernel function such that $K(0) = 1$, $K(x) = 0$ for $|x| > 1$, and $K(x) = K(-x)$. [19] provide additional restrictions on this kernel estimator, but most commonly used kernels satisfy these, such as the rectangular, Bartlett, Parzen, and exponential density kernel among several others. (See, e.g., [20] for formulas for these kernels.) Then [19] show that

$$\sqrt{n}(\hat{\boldsymbol{\gamma}} - \boldsymbol{\gamma}) \xrightarrow{\mathcal{D}} N(\mathbf{0}_{p+1}, V), \tag{4}$$

(for V, see original paper). Finite sample inference can be obtained by

$$\hat{\boldsymbol{\gamma}} \dot{\sim} N(\boldsymbol{\gamma}, \widehat{V}), \text{ for } \widehat{V} := n(\widehat{Z}'\widehat{Z})^{-1}Z'H(H'H)^{-1}\widehat{\Psi}(H'H)^{-1}H'Z(\widehat{Z}'\widehat{Z})^{-1}. \tag{5}$$

[†]Notable among the details in the original papers are the following two assumptions: (1) the diagonal elements of the adjacency matrix are zero, and (2) the network autocorrelation parameter ρ is less than one in absolute value.

3 | NETWORK INTERVENTION STUDY DESIGN

3.1 | Analytical framework

We emphasize that the focus here is not on determining the treatment effect on an individual actor, but rather the effect on the entirety of the network due to the network intervention, where the network intervention consists of both the actor-level treatment and the treatment assignation itself. In this sense we have a "n of one" problem as there is only one network on which to apply the network intervention. We are thus necessarily constrained to a pre- post- test study design in the hopes of measuring some change due to the intervention. That is, we first observe $\boldsymbol{y}_0$, X_0, and A_0, and we then implement a treatment to some fraction of the actors while continuing to observe $\boldsymbol{y}_1$, X_1, and A_1.

In this context, whatever statistical framework is used must account for the temporal dependencies that will exist in the data. Much recent attention has been paid to panel data with network correlated errors, primarily in the spatial literature ([21] as an exception). As the focus of the overwhelming majority of the literature is driven by spatial adjacencies rather than network adjacencies, in these works the network is assumed symmetric and fixed over time, i.e., $A_0 = A_1$. The dependence structure is most often assumed to be compound symmetry ([22,23,24,25]). In some cases temporal autoregressive terms are combined with random actor effects ([26,27]) or fixed actor effects ([28,27]). [29] used both fixed actor and fixed time effects.

We opt instead for the very general framework of KP07 described above in Section 2.2, although this work was not originally intended for longitudinal data. This framework does not require specification of the temporal dependence structure or of the underlying distribution of the errors, nor must we assume homoscedasticity; additionally, the estimators do not require the network to be time invariant.

To see how our pre-post data analysis fits within KP07, first let $\boldsymbol{u}$ denote the $n \times 1$ treatment assignation vector such that $\boldsymbol{u}_i = 1$ if treatment is applied to actor i and zero otherwise. Let $1_{\{\cdot\}}$ be the indicator function equaling one if its expression is true and zero otherwise, and let the subscript k equal 0 for pre-intervention and 1 for post-intervention. Then we assume the data are generated according to

$$\boldsymbol{y}_k = X_k\boldsymbol{\beta} + \tau\boldsymbol{u}1_{\{k=1\}} + \rho A_k\boldsymbol{y}_k + \boldsymbol{\epsilon}_k, \tag{6}$$

We shall refer to the quantity τ as the *isolated treatment effect* (ITE); that is, if we were to eliminate the contamination effect through A_k, τ gives the change in the expected response value under treatment. Let $\tilde{\boldsymbol{y}} := (\boldsymbol{y}_0', \boldsymbol{y}_1')'$, $\tilde{\boldsymbol{\epsilon}} := (\boldsymbol{\epsilon}_0', \boldsymbol{\epsilon}_1')'$, and let $\tilde{A}$ be the block diagonal matrix formed from A_0 and A_1. Then we have a NAM given by

$$\begin{aligned} \tilde{\boldsymbol{y}} &= \widetilde{X}\tilde{\boldsymbol{\beta}} + \rho\tilde{A}\tilde{\boldsymbol{y}} + \tilde{\epsilon}, \quad \tilde{\epsilon} \sim (\boldsymbol{0}_{2n}, \Sigma) \\ \text{where } \widetilde{X} &:= \begin{pmatrix} X_0 & \boldsymbol{0}_n \\ X_1 & \boldsymbol{u} \end{pmatrix}, \\ \text{and } \tilde{\boldsymbol{\beta}} &:= (\boldsymbol{\beta}', \tau)'. \end{aligned} \tag{7}$$

Estimation and inference may proceed as in the static context.

The covariance of the noise $\tilde{\epsilon}$, Σ, can be any $2n \times 2n$ positive-definite covariance matrix. While we are not obligated to constrain any element of Σ to be zero, in the context of heteroscedastic longitudinal data it seems reasonable to assume that

$$\mathrm{Cov}(\tilde{\epsilon}_\ell, \tilde{\epsilon}_m) \begin{cases} > 0 \text{ if } \ell = m \\ \geq 0 \text{ if } |\ell - m| = n \\ = 0 \text{ otherwise.} \end{cases} \tag{8}$$

(Note that while there is no correlation assumed among the random perturbations $\boldsymbol{\epsilon}_k$, there is still non-zero correlation between the observations $\boldsymbol{y}_k$, as the covariance of $\boldsymbol{y}_k$ is given by the potentially dense corresponding block in $(I_{2n} - \rho\tilde{A})^{-1}\Sigma(I_{2n} - \rho\tilde{A}')^{-1}$.) Thus a reasonable dissimilarity matrix passed into the kernel estimator of Ψ in (3) might correspond to

$$\begin{pmatrix} 0 & 1-\delta \\ 1-\delta & 0 \end{pmatrix} \otimes I_n + (1+\delta)J_2 \otimes (J_n - I_n), \tag{9}$$

for some $0 < \delta < 1$ where $J_m = \mathbb{1}_m\mathbb{1}_m'$ and $\mathbb{1}_m$ is the $m \times 1$ column vector of ones. This dissimilarity matrix yields a value of zero for $i = j$ at the same time point, thus leading to a kernel value of 1, the value $1 - \delta$ for $i = j$ at different time points leading to a kernel value between 0 and 1, and a value of $1 + \delta$ for any $i \neq j$ leading to a kernel value of 0.

As alluded to previously, the quantity of interest is not necessarily the isolated treatment effect (or at least is not *primarily* that). Instead, we are more interested in global changes. To capture this, we define the *conditional total treatment effect* for an

adjacency matrix A and treatment assignation $\boldsymbol{u}$ to be

$$cTTE_A(\boldsymbol{u}) := \sum_{i=1}^{n} \left[\mathbb{E}(\boldsymbol{y}_i|X,\boldsymbol{u},A) - \mathbb{E}(\boldsymbol{y}_i|X,\boldsymbol{0}_n,A)\right] = \tau \mathbb{1}_n'(I_n - \rho A)^{-1}\boldsymbol{u}. \tag{10}$$

Using the delta method, it can be shown that the estimator for $cTTE(A)$ is asymptotically distributed as

$$\begin{aligned}\sqrt{n}(\widehat{cTTE}_A(\boldsymbol{u}) - cTTE_A(\boldsymbol{u})) &\xrightarrow{\mathcal{D}} N(\boldsymbol{0}_{p+1}, (\nabla cTTE)' V_{\tau,\rho}(\nabla cTTE)), \\ \text{for } \nabla cTTE &= \left(\mathbb{1}_n'(I_n - \rho A)^{-1}\boldsymbol{u}, \tau \mathbb{1}_n'(I_n - \rho A)^{-1}A(I_n - \rho A)^{-1}\boldsymbol{u}\right),\end{aligned} \tag{11}$$

where $V_{\tau,\rho}$ is the appropriate 2×2 submatrix of V. Finite inference can be made via

$$\begin{aligned}\widehat{cTTE}_A(\boldsymbol{u}) &\dot{\sim} N(cTTE_A(\boldsymbol{u}), (\widehat{\nabla cTTE})' \widehat{V}_{\tau,\rho}(\widehat{\nabla cTTE})), \\ \text{for } \widehat{\nabla cTTE} &= \left(\mathbb{1}_n'(I_n - \hat{\rho}A)^{-1}\boldsymbol{u}, \hat{\tau}\mathbb{1}_n'(I_n - \hat{\rho}A)^{-1}A(I_n - \hat{\rho}A)^{-1}\boldsymbol{u}\right).\end{aligned} \tag{12}$$

Consider the case where the network configuration is highly dynamic, i.e., the network connectivity patterns change frequently between different time points. In such contexts the clinical significance of $cTTE$ may be diminished, as the effect corresponding to the set of edges at one specific time point may not be of particular use. That is, we don't necessarily care about the total effect on the network at a particular moment in time as that moment is unlikely to be repeated exactly, but rather we care about the expected total effect on the network at any given time, where the expectation is taken over the varying connectivities of the networked actors. Suppose that we have a marginal postulated probability distribution over the network A at any given time point, i.e., $\pi(A_k)$. There is a massive amount of literature on possible data generating mechanisms for networks, the primary ones including the exponential random graph model[30], latent space models[31], and stochastic blockmodels[32]. We then define the *marginal total treatment effect* for a treatment assignation $\boldsymbol{u}$ as

$$\begin{aligned}mTTE(\boldsymbol{u}) &:= \sum_{i=1}^{n} \left[\mathbb{E}(\boldsymbol{y}_i|X,\boldsymbol{u}) - \mathbb{E}(\boldsymbol{y}_i|X,\boldsymbol{0}_n)\right] \\ &= \mathbb{E}(cTTE_A(\boldsymbol{u})) \\ &= \tau \mathbb{1}_n' \mathbb{E}\Big((I_n - \rho A)^{-1}\Big)\boldsymbol{u}. \\ &= \tau \mathbb{1}_n' \left(I_n + \sum_{\ell=1}^{\infty} \rho^\ell \mathbb{E}(A^\ell)\right)\boldsymbol{u}.\end{aligned} \tag{13}$$

Note that this last equality is based on the Neumann series and holds only if $\lim_{\ell\to\infty} \rho^\ell A^\ell = \boldsymbol{0}$ ([33], p.55). This condition is satisfied if, for example, ρ is less than the inverse of the maximum eigenvalue of A, or if $\|\rho A\|_\infty < 1$ (where $\|M\|_\infty := \max_i \sum_j |M_{ij}|$).

As a pedagogical example, suppose A_k is a simple undirected graph, and the marginal distribution of A_k follows a stochastic blockmodel with b blocks, $b \times b$ edge probability matrix B, and $n \times b$ block assignment W. That is, $\mathbb{P}(A_{k,ij} = 1) = W_i B W_j'$. This might arise if, e.g., researchers are implementing a vaccination campaign across a region consisting of several villages, where each village member has a certain high probability of interacting with others from the same village and some low probability of interacting with those from other villages. It can be shown that under the assumptions of the stochastic blockmodel

$$\mathbb{E}(A_k^\ell) = (WBW')^\ell,$$

and hence by using a partial sum approximation of (13) we can compute the $mTTE$. In cases where the distribution of the network is more complicated, e.g., an exponential random graph model, one can use a Monte Carlo approximation of (13).

Just as before with $cTTE(A)$, we may make finite inference on $mTTE$ via

$$\begin{aligned}\widehat{mTTE}(\boldsymbol{u}) &\dot{\sim} N(mTTE(\boldsymbol{u}), (\widehat{\nabla mTTE})' \widehat{V}_{\tau,\rho}(\widehat{\nabla mTTE})), \\ \text{for } \widehat{\nabla mTTE} &= \left(\mathbb{1}'\left(I + \sum_{\ell=1}^{\infty} \hat{\rho}^\ell \mathbb{E}(A^\ell)\right)\boldsymbol{u}, \hat{\tau}\mathbb{1}\left(\sum_{\ell=1}^{\infty} \ell \hat{\rho}^{\ell-1} \mathbb{E}(A^\ell)\right)\boldsymbol{u}\right).\end{aligned} \tag{14}$$

3.2 | Power analysis

Unlike the MLE or Bayesian estimators, the IV estimators provide a closed form solution that facilitates much easier power calculations. One aspect of this that requires some comment is that the covariance matrix for $\hat{\boldsymbol{\gamma}}$ in (4) involves $\boldsymbol{y}$ and $\widehat{\Psi}$. Now

$\widehat{\Psi}$ is a consistent estimator and so we may reasonably replace $\widehat{\Psi}$ in (4) with the true Ψ. For example, if an AR(1) correlation structure is appropriate, then we may use

$$\Psi = \frac{1}{n} H' \left(\sigma^2 \mathcal{T}_\phi \otimes I_n\right) H,$$
$$\text{where } \left[\mathcal{T}_\phi\right]_{ts} = \phi^{|t-s|} \quad \text{for } \phi \in (-1, 1)$$

for some variance σ^2 and temporal correlation parameter ϕ. Replacing Z with $(\widetilde{X}, \tilde{A}(I - \rho\tilde{A})^{-1}\widetilde{X}\tilde{\beta})$ then allows us to obtain a good approximation of the sampling distribution used to evaluate the study's power.

The explicit solutions to conducting a power analysis can be found in the typical way for normal sampling distributions. For example, evaluating power for a one-sided level α test is

$$\text{Power} = \Phi\left(\frac{|\tau|}{\sqrt{\widehat{V}_{\tau,\tau}}} - \Phi^{-1}(1-\alpha)\right), \tag{15}$$

where Φ is the standard normal cumulative distribution. Note that one could just as easily compute the power to detect a certain $cTTE(A)$ or $mTTE$ using (12) or (14). However, when comparing multiple possible treatment assignations, it is advisable to focus on the ITE despite the ITE not necessarily being the quantity of interest. See Section 5.3 for more explanation.

3.3 | Optimal treatment assignation

Up to this point we have made no mention of how to choose the treatment assignation $\boldsymbol{u}$. Intuitively, if the goal of the study is to leverage the network topology to augment the effect of treating a certain number of actors, then we ought to look for a smaller set of "important" actors. This sense of importance can be and has been defined in numerous ways. One of the most straightforward ways to choose these actors is to compute some centrality measure such as degree centrality or betweenness centrality on each actor and choose the top k actors.[34] used this approach in designing effective vaccination strategies, and[35] used this approach in studying the spread of HAIs. A tweak on this approach is to recalculate the centrality measure each time an actor is included in the importance set[36]. More sophisticated approaches have been developed to disrupt networks[37,38]. Perhaps the best known work in this area is that of the Key Players Problem (KPP)[39]. There have been quite a number of algorithmic developments to better optimize or extend the original work on KPP e.g.,[40,41,42,43]. Many of these works are limited to simple undirected graphs, which is too limiting in our context. These works also fail to account for the case where the cost of treatment may differ from actor to actor.

It turns out that for our proposed study design we can find an optimal solution. By optimal, we mean in the sense that we can maximize the effect on the response variable of all actors of the network due to treating a subset of the actors, the selection of which is subject to some total cost of treatment. The total effect on the network due to the treatment is captured directly in $cTTE_A(\boldsymbol{u})$ for some specific A or for $mTTE$ otherwise. For the purposes of discourse we will focus on the $cTTE_A(\boldsymbol{u})$; extending to $mTTE$ is trivial. First, define the *total treatment effect coefficient* for an adjacency matrix A and treatment assignation $\boldsymbol{u}$ as

$$TTEC_A(\boldsymbol{u}) = \mathbb{1}_n'(I_n - \rho A)^{-1}\boldsymbol{u}. \tag{16}$$

Then to put the problem formally, we wish to find $\boldsymbol{u}^*$ such that

$$\boldsymbol{u}^* = \underset{\boldsymbol{u}\in\{0,1\}^n}{\text{argmax}}\left\{TTEC_A(\boldsymbol{u})\right\} \text{ subject to } \boldsymbol{c}'\boldsymbol{u} \le C, \tag{17}$$

where $\boldsymbol{c}$ is a $n\times 1$ vector of actor-specific costs and C is the maximum cost allowed, i.e., the spending limit. Then for any isolated treatment effect τ (assuming the correct sign of τ to achieve the desired result) the optimal treatment assignation $\boldsymbol{u}^*$ can be found using a binary linear programming algorithm e.g., using[44].

Those familiar with network measures may recognize the $TTEC_A(\boldsymbol{u})$ as a function of the actors' Katz centralities, where centrality is based on outgoing rather than incoming edges. Hence the optimal $\boldsymbol{u}$ finds those actors with highest Katz centrality subject to a set of cost constraints.

As an illustration, we simulated a simple undirected network with 50 actors according to a preferential attachment model. We then set A to be the row-normalized adjacency matrix and set $\rho = 0.15$. Figure 1 shows this network graphically. The size of the nodes corresponds to the values of the n-dimensional vector $\mathbb{1}_n'(I_n - \rho A)^{-1}$. The top five nodes that optimize the $TTEC$ are shown as hollow circles; all others are shown as solid.

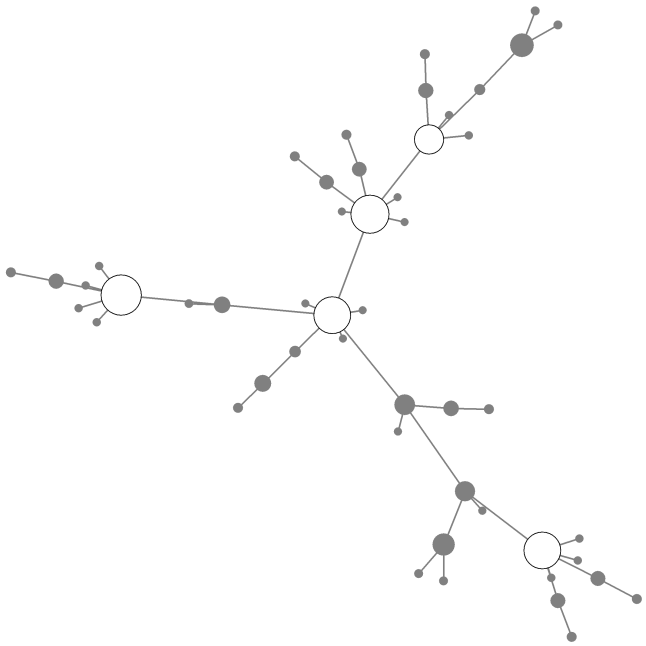

FIGURE 1 Small toy example using 50 actors in a preferential attachment model. Node size corresponds to the elements of $\mathbb{1}'(I-\rho A)^{-1}$. The top five nodes that optimize the $TTEC$ are shown as hollow circles, all others are solid.

3.4 | Interactions with the treatment

In some situations, the treatment may not have a direct additive effect or may not be restricted to only such an effect but may instead influence the way in which other factors affect the response. We will see an example of this in Section 5. Suppose we can partition our covariates into $X_k = (X_{k(0)}, X_{k(1)})$, where it is only the set of variables contained in $X_{k(1)}$ for which the effect on $\boldsymbol{y}_k$ will be influenced by the treatment. (Note that $X_{k(1)}$ may include the intercept to account for a main treatment effect.) In this case we have

$$\begin{aligned} \tilde{\boldsymbol{y}} &= \check{X}\check{\boldsymbol{\beta}} + \rho\tilde{A}\boldsymbol{y} + \tilde{\boldsymbol{\epsilon}}, \quad \tilde{\boldsymbol{\epsilon}} \sim (\mathbf{0}_{2n}, \Sigma), \\ \text{where } \check{X} &:= \begin{pmatrix} X_{0(0)} & X_{0(1)} & \mathbf{0} \\ X_{1(0)} & X_{1(1)} & D_u X_{1(1)} \end{pmatrix}, \\ D_u &:= \text{Diag}(\boldsymbol{u}), \\ \text{and } \check{\boldsymbol{\beta}} &:= \begin{pmatrix} \boldsymbol{\beta}_0' & \boldsymbol{\beta}_1' & \boldsymbol{\tau}' \end{pmatrix}', \end{aligned} \tag{18}$$

and where $\text{Diag}(\boldsymbol{v})$ is the diagonal matrix with entries given by the vector $\boldsymbol{v}$. Also note that $\boldsymbol{\tau}$ is a column vector with length equal to the number of columns of $X_{k(1)}$.

In this context of treatment-covariate interactions, the conditional total treatment effect is given by

$$\begin{aligned} cTTE_{A,X}(\boldsymbol{u}) &:= \sum_i \left[\mathbb{E}(\boldsymbol{y}_{t,i}|X_{(0)}, X_{(1)}, \boldsymbol{u}, A) - \mathbb{E}(\boldsymbol{y}_{t,i}|X_{(0)}, X_{(1)}, \mathbf{0}_n, A)\right] \\ &= \mathbb{1}_n'(I_n - \rho A)^{-1}\text{Diag}(\boldsymbol{u})X_{(1)}\boldsymbol{\tau}, \end{aligned} \tag{19}$$

Letting $\mathbf{m}' := \mathbb{1}_n'(I_n - \rho A)^{-1}$, we can see that the $cTTE_{A,X}(\boldsymbol{u})$ is symmetric in $\mathbf{m}$ and $\boldsymbol{u}$. Hence we may alternatively write

$$cTTE_{A,X}(\boldsymbol{u}) = \left(\text{Diag}(\mathbf{m})X_{(1)}\boldsymbol{\tau}\right)'\boldsymbol{u}. \tag{20}$$

Writing the $cTTE_{A,X}(\boldsymbol{u})$ in this manner lends itself to the same binary linear programming algorithm as before in order to find the optimal treatment assignation $\boldsymbol{u}^*$ for a specific $\boldsymbol{\tau}$ and $X_{(1)}$. If $X_{(1)}$ consists of two or more variables, $\boldsymbol{u}^*$ may depend on $\boldsymbol{\tau}$. If $X_{(1)}$ is a single covariate, then assuming τ has the sign corresponding to the desired result, we may remove τ from the

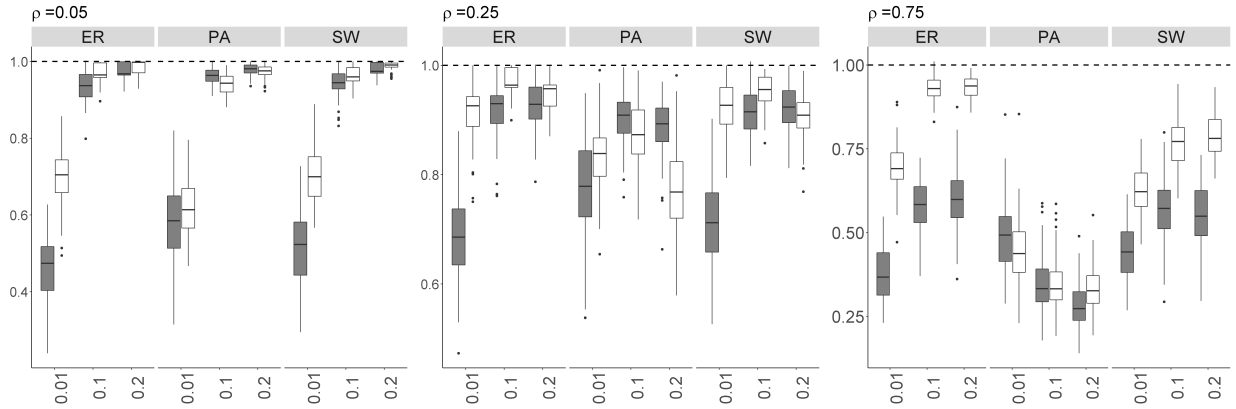

FIGURE 2 Simulation study results from 100 simulations for each of three network generation mechanisms, three network densities (horizontal exis), and three values of ρ (panels). Displayed are boxplots of ratios of TTECs comparing the use of betweenness centrality (dark) and degree centrality (light) as treatment assignation strategies vs. the proposed optimal strategy.

$cTTE_{A,X}(\boldsymbol{u})$ to obtain the $TTEC_{A,X}(\boldsymbol{u})$ to be used in finding $\boldsymbol{u}^*$. For the marginal total treatment effect, we may repeat the above while setting $\mathbf{m}' := \mathbb{1}_n' \left(I_n + \sum_{\ell=1}^{\infty} \rho^{\ell} \mathbb{E}(A^{\ell}) \right)$.

4 | SIMULATION STUDY

We ran a simulation study to evaluate our proposed treatment assignation strategy on the total change in the response due to a treatment effect. This total change was measured in terms of the TTEC, as the ITE would only rescale this value. We compared our assignation strategy to that obtained by either using the vector of betweenness centrality measures or degree centrality measures as coefficients in (20) rather than $\mathbb{1}'(I - \rho A)^{-1}$. We simulated networks with 100 actors according to three different graph generating mechanisms: (1) Erdös Rényi random graph (ER), (2) preferential attachment (PA), and (3) small world (SW). We tried three different values of ρ (0.05, 0.25, and 0.75) and three different density values (0.01, 0.1, and 0.2).

The ER graphs were generated by randomly assigning edges to pairs of actors. The PA graphs were generated by sequentially adding actors to the graph and connecting them to a random number of other actors drawn from a Poisson distribution with mean yielding the desired density, choosing these connections with probability proportional to their current degree. The SW graphs were generated by creating a circular lattice, and then rewiring each edge randomly with probability 0.1.

When computing the TTEC, each network was row-normalized. Since the absolute magnitude of the TTEC is unimportant for the purposes of a simulation study, we divided each strategy's TTEC by that of the proposed optimal strategy. Figure 2 shows boxplots of the relative TTECs over the different ρ, density, and network configurations. These results indicate that the proposed treatment assignation always provided the largest network-wide change in response (as expected), and the network structure, density, and ρ value play a role in whether degree or betweenness centrality is second best. More interestingly, the network density seems to have a large effect on just how much better the optimal treatment assignation is than these other reasonable alternatives. In addition, in the presence of a strong network effect ($\rho = 0.75$), the fact that the proposed approach is dramatically better for the PA networks for all densities seems to indicate that the optimal treatment assignation will have greater improvements on the total network-wide change for tree-like networks.

5 | PATIENT SHARING NETWORK

5.1 | Background

Hospital acquired infections are a major source of morbidity, mortality and healthcare costs.[45] estimated that in 2002 there were 1.7 million HAIs in U.S. hospitals leading to 98,987 deaths.[46] found that five types of HAIs led to $9.8 billion in 2012. It is thus of paramount importance to reduce these HAIs and their impact. Local interventions, however, have met with limited success e.g.,[47,48].

TABLE 1 Estimates from fitting a NAM to the California CDI data.

	Est	LB	UB	p-value
Intercept	-5.3	-6.4	-4.2	< 0.001
Total admissions	0.0065	0.0055	0.0075	< 0.001
Median LOS	0.015	-0.056	0.087	0.34
Median # dx	0.56	0.41	0.71	< 0.001
% over 65	1.7	-0.13	3.6	0.034
ρ	0.16	0.068	0.25	< 0.001

It is widely recognized that a critical component of the spread of HAIs is patient sharing between hospitals.[49],[50] and[51] found genetic evidence that patient sharing is an important transmission vector of HAIs. In some instances an outbreak has been linked to a specific transfer patient[52,53,54]. Statistical approaches have been used to provide evidence as well e.g.,[55,56], as well as simulation studies e.g.,[57,58]. It is thus of no surprise that many are arguing for regional, rather than local, intervention strategies to reduce the number of HAI cases[59,60,61,62,63].

5.2 | Preliminary analysis

We analyzed *Clostridium difficile* infection (CDI) data using the Healthcare Utilization Project State Inpatient Database for California during the years 2005 to 2011 involving 26,879,277 inpatient admissions. We considered 385 hospitals involving 162,286 secondary CDI cases (we did not consider primary diagnoses of CDI as these were community based, rather than hospital acquired). We defined a patient transfer to occur when a patient is discharged from one hospital and admitted into another on the same day. This led to 532,925 patient transfers.

Following[64], we fit a static NAM using as a response variable the monthly average number of CDI cases and as covariates the monthly average number of admissions, the median length of stay, the median number of diagnoses, and the proportion of patients over 65. The adjacency matrix A was constructed such that A_{ij} was the monthly average number of transfers from j to i divided by the monthly average number of admissions in hospital j (the diagonal elements A_{ii} were fixed at zero); we row-normalized the adjacency matrix when fitting the NAM. We used $\left(X \;\; AX \;\; A^2X\right)$ as the instrument matrix, which had an adjusted R^2 in the first stage (regressing $A\boldsymbol{y}$ on the instrument matrix) of 0.963, indicating a strong instrument. Table 1 provides the parameter estimates as well as confidence intervals and p-values for $H_0 : \boldsymbol{\gamma} = \mathbf{0}$ for fitting the NAM to the California data.

5.3 | Study design

To illustrate the proposed study design, we consider the context where the monthly average number of CDI cases is measured both before and after a hypothetical intervention is implemented at a subset of hospitals. While the network is technically dynamic, for the purpose of planning the study we assume that the network is static. This is a reasonable assumption as the network connectivities are highly correlated from one month to the next. However, if after completion of the study the patient transfer patterns exhibited clinically meaningful differences, a network model could be fit in order to estimate the $mTTE$, and the pre- and post-intervention networks could be used to construct the block diagonal matrix $\tilde{A}$ in (7) as described in Section 3.1.

It is unrealistic to think that a treatment applied to hospitals of dramatically different sizes will lead to an equivalent reduction in the number of CDI cases. Rather, it is more reasonable to assume that a treatment will be able to reduce the *proportion* of CDI cases at the treated hospital. It is therefore more appropriate to consider the interaction between the treatment and total admission rather than simply a direct treatment effect; i.e., the treatment will reduce the proportion of total admissions that contribute to the total CDI case count. We thus use the approach given in Section 3.4.

We assumed that the cost of treating a particular hospital corresponded directly with the number of beds at that hospital, and for the purposes of a pedagogical example we also assumed that we can treat up to 5% of the beds of all hospitals in the network. The treatment only interacts with one covariate (monthly total admissions), and so as long as the treatment does in fact reduce rather than increase the percent of total admissions to result in a CDI, we can find the treatment assignation that optimizes the $TTEC_{A,X}(\boldsymbol{u})$. Setting A to be the observed patient sharing network, $X_{(0)}$ to be the median LOS, median number of diagnoses per patient, and percent over 65, $X_{(1)}$ to be the monthly average total admissions, and ρ to be the estimated network coefficient

of 0.16 we computed the optimal treatment assignments. Figure 3 shows the patient sharing network using the Fruchterman-Reingold layout; those hospitals to be treated are shown as hollow circles, all others are solid. As was done in the simulation study, we also found treatment assignations subject to the same cost constraints using binary linear programming as before but using the vector of betweenness centrality measures (triangle overlays) as coefficients in (20), as well as using the vector of degree centrality measures (square overlays).

We next computed the power of detecting a statistically significant treatment effect in terms of ITE. In this context, the ITE corresponds to the reduction in the proportion of the total number of admissions that result in a CDI were it possible to completely isolate the hospital from patient transfers. Figure 4 shows the power for each ITE. The power was estimated assuming an AR(1) structure on the residuals over time with autoregressive parameter equal to 0.5 (see Section 3.2). The optimal treatment assignation clearly dominates, while the assignations based on degree and betweenness centrality yield indistinguishable power curves. As a specific example, we would have 80% power to detect an ITE of 0.0011; assigning treatment according to betweenness centrality (dashed-dotted line) yields 74% power to detect this same ITE, and assigning treatment according to degree centrality (dotted line) only yields 75% power to detect this same ITE.

Despite the fact that it is the $cTTE_{A,X}(\boldsymbol{u})$ that we care about, power should be viewed in terms of the ITE rather the $cTTE_{A,X}(\boldsymbol{u})$, which in our context corresponds to the total region-wide reduction in the number of CDI cases due to applying treatment to all hospitals in the optimal treatment group. This is because for a fixed power level, a poor treatment assignation will be powered to detect a lower $cTTE_{A,X}(\boldsymbol{u})$ than a good treatment assignation due to the fact that a much higher ITE is necessary to achieve this lower $cTTE_{A,X}(\boldsymbol{u})$ using the poorer assignation. Put another way, a poorer assignation requires a much stronger treatment effect to attain the same $cTTE_{A,X}(\boldsymbol{u})$ as a better assignation. In fact it is because the better treatment assignation yields a higher $cTTE_{A,X}(\boldsymbol{u})$ than the poorer assignation (more "bang for your buck") that it is more powered. The relationship between ITE and $cTTE_{A,X}(\boldsymbol{u})$ is illustrated for our context in Figure 5, where for each ITE value the corresponding $cTTE_{A,X}(\boldsymbol{u})$ value is given. From this we see that the total gains can be quite substantial by using an optimal design even when compared with reasonable alternatives. The gray lines correspond to the point at which we achieve 80% power for each treatment assignation, illustrating how one must compare power across treatment assignations via ITE rather than $cTTE_{A,X}(\boldsymbol{u})$.

Finally, we investigated how the region-wide treatment effect would change as we vary the proportion of hospital beds we can afford to treat. Figure 6 shows this in terms of the $TTEC_{A,X}(\boldsymbol{u})$ using the optimal treatment assignation divided by the $TTEC_{A,X}(\mathbb{1})$ attained by treating all hospitals (solid line). This allows us to view the proportion of the total possible reduction in CDI cases attained by treating a proportion of the hospital beds vs. the proportion of the hospital beds treated. The dotted line is the $y = x$ line, i.e., where treating, e.g., 50% of the hospital beds would lead to 50% of the maximum possible reduction in CDI cases. The concave shape to the curve demonstrates that there is a gain in efficiency by strategically choosing the hospitals to treat. The gray lines give the deciles of the proportion of the maximum reduction in CDI cases, and from this we see, for example, that we can attain 50% of the maximum reduction in CDI cases by actually treating around 35% of the hospital beds.

6 | CONCLUSION

Diffusion through a network can affect things such the spread of disease or information dissemination, and influence through social network connections can change individuals' behaviors in profound ways. Though this paper was specifically motivated by the urgent need for a regional approach to diminish HAIs, the proposed framework provides the tools to plan an intervention on any set of subjects or objects connected in some meaningful way through a measurable network. This work is a starting point for designing and planning for studies aimed at intervening on a network, but several future directions ought to be undertaken. First, in computing the $mTTE(\boldsymbol{u})$ we have assumed the model parameters of the network generating mechanism are known, whereas in reality these parameters will typically need to be estimated, and that uncertainty ought to be accounted for. Second, we have assumed a continuous outcome, and these methods may need to be adapted non-trivially depending on the discrete nature of the outcome. Third, the treatment assignation procedure as described was based on a known static network; while it is beyond the scope of this work, it would be very worthwhile exploring the effects, especially on power, of needing to find the optimal treatment assignation $\boldsymbol{u}$ based on A_0 or an estimate of the unknown A_1. Finally, there may be confounding factors in a pre-post study design that need to be addressed such as contemporaneous effects of innovations in practice and policy that may account for some or all of the observed change[65]. While it is important to continue to study and resolve these issues, this work provides a starting point for developing study designs that investigate the effect of an intervention applied to a subset of network actors on the network as a whole.

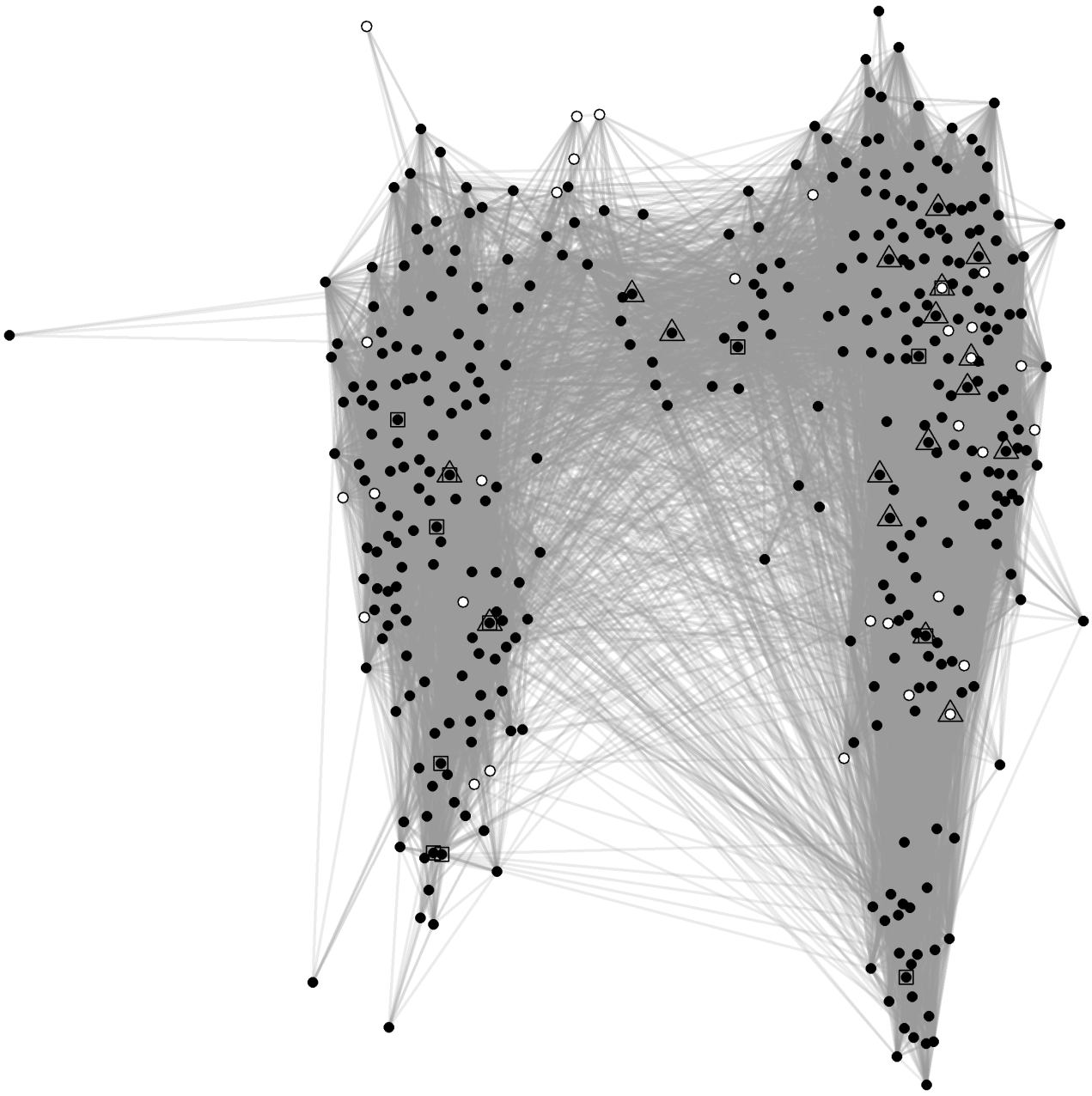

FIGURE 3 CA patient transfer network. The hospitals to be treated according to the optimal treatment assignation are shown as hollow circles, all others are shown as solid. Hospitals to be treated according to betweenness (degree) centrality is given by overlayed triangles (squares).

ACKNOWLEDGMENTS

This work was supported by the US Centers for Disease Control and Prevention (5 U01 CK000531-02). Special thanks to the specific members of the MInd-Healthcare Program: Prabasaj Paul and Rachel Slayton for presentations and group discussions on HAI spread through patient transfers which helped motivate this work, and to Philip M. Polgreen for related discussions both motivating and shaping this work.

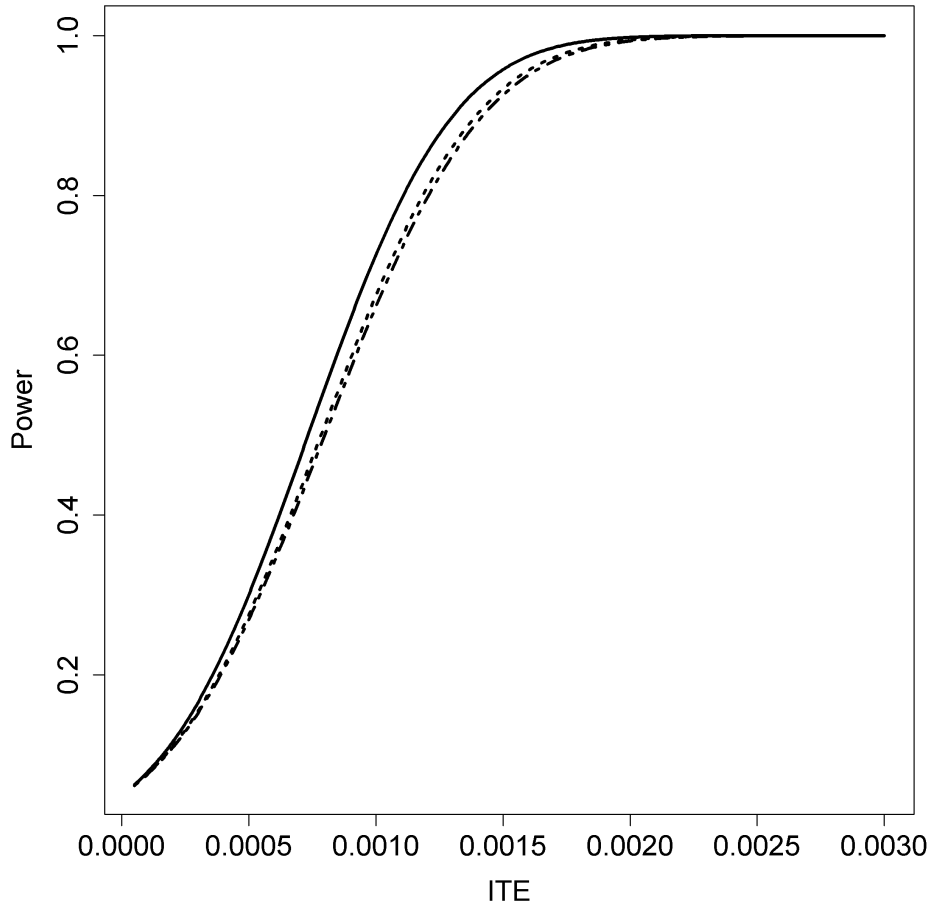

FIGURE 4 Power analysis for a treatment to reduce CDI cases in CA hospitals. Solid line corresponds to optimal treatment assignation, dotted and dashed-dotted lines correspond to choosing the hospitals with the highest betweenness and degree centralities respectively.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Healthcare Cost and Utilization Project. Restrictions apply to the availability of these data, which were used under license for this study.

References

1. Nickerson DW. Is Voting Contagious? Evidence from Two Field Experiments. *American Political Science Review* 2008; 102(1): 49âĂŞ57. doi: 10.1017/S0003055408080039

2. Cox DR. *Planning of Experiments*. New York: Wiley . 1958.

3. Rubin DB. Randomization Analysis of Experimental Data: The Fisher Randomization Test Comment. *Journal of the American Statistical Association* 1980; 75(371): 591-593.

4. Centola D. The Spread of Behavior in an Online Social Network Experiment. *Science* 2010; 329(5996): 1194–1197. doi: 10.1126/science.1185231

5. Miguel E, Kremer M. Worms: Identifying Impacts on Education and Health in the Presence of Treatment Externalities. *Econometrica* 2004; 72(1): 159-217.

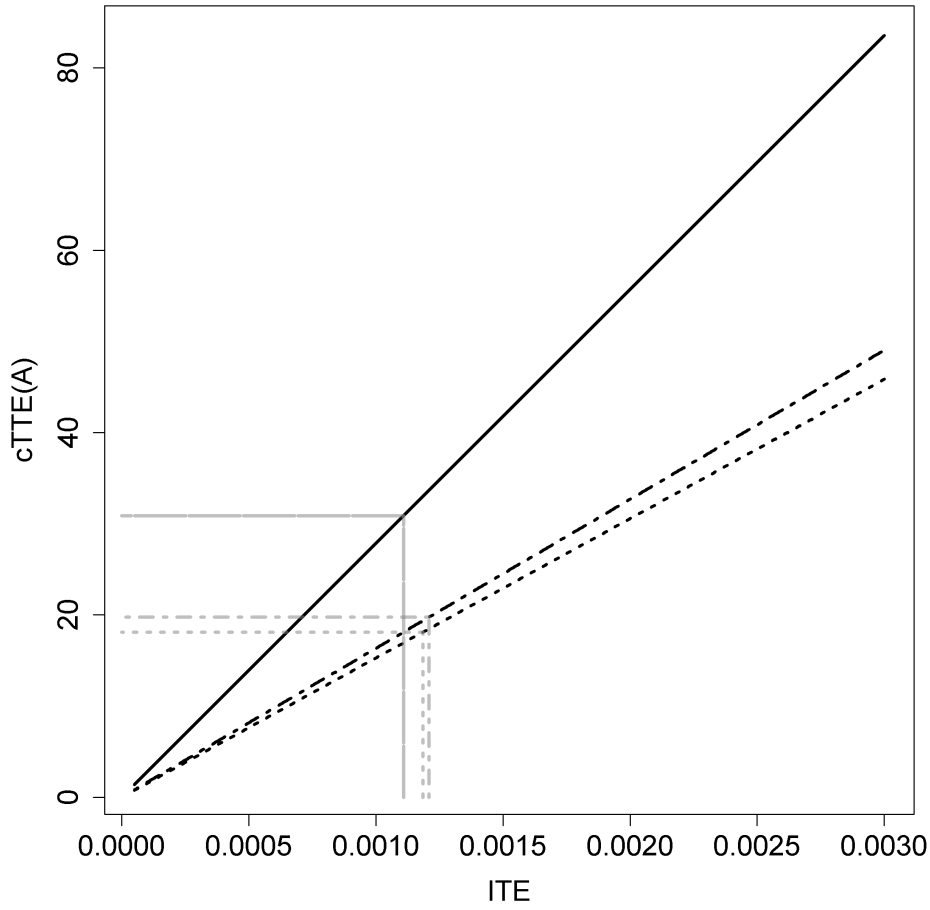

FIGURE 5 Comparison of total network change ($cTTE(A)$) vs. hospital-specific change (ITE). The optimal design is given by the solid line, treatment assignation based on betweenness (degree) centrality is given by the dashed-dotted (dotted) line. Gray lines correspond to the point at which we achieve 80% power. E.g., for the optimal treatment assignation we have 80% power to detect a ITE of 0.0013 and $cTTE(A)$ of 43.

6. Hudgens MG, Halloran ME. Toward Causal Inference With Interference. *Journal of the American Statistical Association* 2008; 103(482): 832-842. PMID: 19081744doi: 10.1198/016214508000000292

7. Sinclair B, McConnell M, Green DP. Detecting Spillover Effects: Design and Analysis of Multilevel Experiments. *American Journal of Political Science* 2012; 56(4): 1055–1069. doi: 10.1111/j.1540-5907.2012.00592.x

8. Liu L, Hudgens MG. Large Sample Randomization Inference of Causal Effects in the Presence of Interference. *Journal of the American Statistical Association* 2014; 109(505): 288-301. PMID: 24659836doi: 10.1080/01621459.2013.844698

9. Gallos LK, Liljeros F, Argyrakis P, Bunde A, Havlin S. Improving immunization strategies. *Phys. Rev. E* 2007; 75: 045104. doi: 10.1103/PhysRevE.75.045104

10. Kck R, Brakensiek L, Mellmann A, et al. Cross-border comparison of the admission prevalence and clonal structure of meticillin-resistant Staphylococcus aureus. *Journal of Hospital Infection* 2009; 71(4): 320 - 326. doi: https://doi.org/10.1016/j.jhin.2008.12.001

11. Fujimoto K, Chou CP, Valente TW. The network autocorrelation model using two-mode data: Affiliation exposure and potential bias in the autocorrelation parameter. *Social Networks* 2011; 33(3): 231–243.

12. Doreian P. Linear models with spatially distributed data: Spatial disturbances or spatial effects?. *Sociological Methods and Research* 1980; 9(1): 29–60.

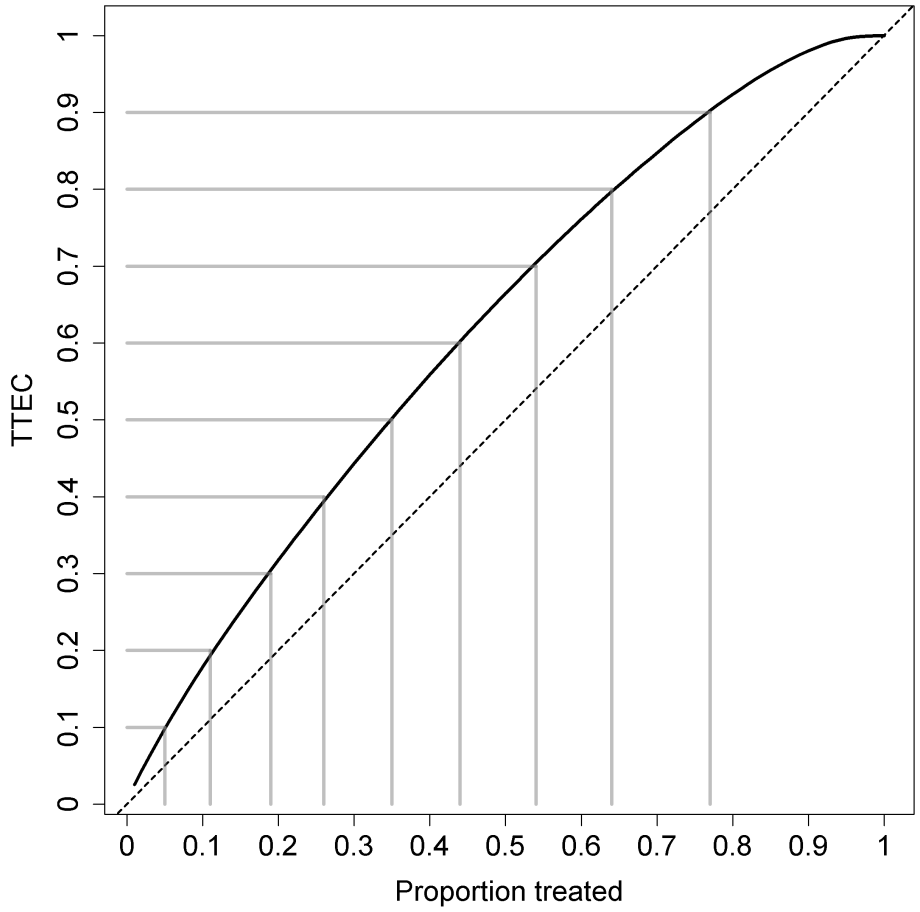

FIGURE 6 TTEC for a treatment to reduce CDI cases in CA hospitals as a function of proportion of hospital beds treated, scaled by the maximum TTEC possible. The solid line corresponds to the optimal treatment assignation; the dotted line corresponds to where the proportion treated equals the proportion of the maximum TTEC attained; gray lines correspond to the deciles of the proportion of the maximum TTEC attained.

13. Doreian P. Estimating linear models with spatially distributed data. *Sociological Methodology* 1981; 12: 359–388.

14. Mizruchi MS, Neuman EJ. The effect of density on the level of bias in the network autocorrelation model. *Social Networks* 2008; 30(3): 190–200.

15. Dittrich D, Leenders RT, Mulder J. Bayesian estimation of the network autocorrelation model. *Social Networks* 2017; 48: 213 - 236. doi: https://doi.org/10.1016/j.socnet.2016.09.002

16. Kelejian HH, Prucha IR. A Generalized Spatial Two-Stage Least Squares Procedure for Estimating a Spatial Autoregressive Model with Autoregressive Disturbances. *The Journal of Real Estate Finance and Economics* 1998; 17(1): 99–121. doi: 10.1023/A:1007707430416

17. Lee Lf. Best Spatial Two-Stage Least Squares Estimators for a Spatial Autoregressive Model with Autoregressive Disturbances.. *Econometric Reviews* 2003; 22(4): 307 - 335.

18. Kelejian HH, Prucha IR, Yuzefovich Y. *Instrumental variable estimation of a spatial autoregressive model with autoregressive disturbances: Large and small sample results*: 163-198; 2004

19. Kelejian HH, Prucha IR. HAC estimation in a spatial framework. *Journal of Econometrics* 2007; 140(1): 131 - 154. Analysis of spatially dependent datadoi: https://doi.org/10.1016/j.jeconom.2006.09.005

20. Andrews DWK. Heteroskedasticity and Autocorrelation Consistent Covariance Matrix Estimation. *Econometrica* 1991; 59(3): 817–858.

21. Hays JC, Kachi A, Franzese RJ. A spatial model incorporating dynamic, endogenous network interdependence: A political science application. *Statistical Methodology* 2010; 7(3): 406 - 428. doi: https://doi.org/10.1016/j.stamet.2009.11.005

22. Kapoor M, Kelejian HH, Prucha IR. Panel data models with spatially correlated error components. *Journal of Econometrics* 2007; 140(1): 97 - 130. Analysis of spatially dependent datadoi: https://doi.org/10.1016/j.jeconom.2006.09.004

23. Baltagi BH, Liu L. Instrumental variable estimation of a spatial autoregressive panel model with random effects. *Economics Letters* 2011; 111(2): 135 - 137. doi: https://doi.org/10.1016/j.econlet.2011.01.016

24. Piras G. Efficient GMM Estimation of a Cliff and Ord Panel Data Model with Random Effects. *Spatial Economic Analysis* 2013; 8(3): 370-388. doi: 10.1080/17421772.2013.804628

25. Badinger H, Egger P. Fixed Effects and Random Effects Estimation of Higher-order Spatial Autoregressive Models with Spatial Autoregressive and Heteroscedastic Disturbances.. *Spatial Economic Analysis* 2015; 10(1): 11 - 35.

26. Su L, Yang Z. QML estimation of dynamic panel data models with spatial errors. *Journal of Econometrics* 2015; 185(1): 230 - 258. doi: https://doi.org/10.1016/j.jeconom.2014.11.002

27. Elhorst JP. Dynamic panels with endogenous interaction effects when T is small. *Regional Science and Urban Economics* 2010; 40(5): 272 – 282. Advances In Spatial Econometricsdoi: https://doi.org/10.1016/j.regsciurbeco.2010.03.003

28. Yu J, Jong dR, Lee fL. Quasi-maximum likelihood estimators for spatial dynamic panel data with fixed effects when both n and T are large. *Journal of Econometrics* 2008; 146(1): 118 - 134. doi: https://doi.org/10.1016/j.jeconom.2008.08.002

29. Lee Lf, Yu J. Efficient GMM estimation of spatial dynamic panel data models with fixed effects. *Journal of Econometrics* 2014; 180(2): 174 - 197. doi: https://doi.org/10.1016/j.jeconom.2014.03.003

30. Lusher D, Koskinen J, Robins G. *Exponential Random Graph Models for Social Networks: Theory, Methods, and Applications*. Structural Analysis in the Social SciencesCambridge University Press . 2012

31. Hoff PD, Raftery AE, Handcock MS. Latent space approaches to social network analysis. *Journal of the American Statistical Association* 2002; 97(460): 1090–1098.

32. Nowicki K, Snijders TAB. Estimation and prediction for stochastic blockstructures. *Journal of the American Statistical Association* 2001; 96(455): 1077–1087.

33. Stewart GW. *Matrix Algorithms Volume I: Basic Decompositions*. Philadelphia: Society for Industrial and Applied Mathematics . 1998.

34. Ueno T, Masuda N. Controlling nosocomial infection based on structure of hospital social networks. *Journal of Theoretical Biology* 2008; 254(3): 655 - 666. doi: https://doi.org/10.1016/j.jtbi.2008.07.001

35. Hornbeck T, Naylor D, Segre AM, Thomas G, Herman T, Polgreen PM. Using sensor networks to study the effect of peripatetic healthcare workers on the spread of hospital-associated infections. *The Journal of Infectious Diseases* 2012; 206(10): 1549-1557. doi: 10.1093/infdis/jis542

36. Holme P, Kim BJ, Yoon CN, Han SK. Attack vulnerability of complex networks. *Physical Review E* 2002; 65: 056109. doi: 10.1103/PhysRevE.65.056109

37. Chen Y, Paul G, Havlin S, Liljeros F, Stanley HE. Finding a better immunization strategy. *Phys. Rev. Lett.* 2008; 101: 058701. doi: 10.1103/PhysRevLett.101.058701

38. Morone F, Makse HA. Influence maximization in complex networks through optimal percolation. *Nature* 2015; 524: 65-68.

39. Borgatti SP. Identifying sets of key players in a social network. *Computational & Mathematical Organization Theory* 2006; 12(1): 21–34. doi: 10.1007/s10588-006-7084-x

40. Ortiz-Arroyo D, Hussain DMA. An Information Theory Approach to Identify Sets of Key Players. In: Ortiz-Arroyo D, Larsen HL, Zeng DD, Hicks D, Wagner G., eds. *Intelligence and Security Informatics*Springer Berlin Heidelberg; 2008; Berlin, Heidelberg: 15–26.

41. Yang J. Generalized key player problem. *Computational and Mathematical Organization Theory* 2015; 21(1): 24–47. doi: 10.1007/s10588-014-9175-4

42. Hung NT, Viet HT. Identifying key player using sum of influence probabilities in a social network. In: Dang TK, Wagner R, Küng J, Thoai N, Takizawa M, Neuhold EJ., eds. *Future Data and Security Engineering*Springer International Publishing; 2017; Cham: 444–452.

43. Wu W, Chan WKV, Chi L, Gong Z. Identifying a set of key members in social networks using SDP-based stochastic search and integer programming algorithms. *Asia-Pacific Journal of Operational Research* 2017; 34(03): 1750002. doi: 10.1142/S0217595917500026

44. Berkelaar M, Eikland K, Notebaert P. lp_solve 5.5, Open source (Mixed-Integer) Linear Programming system. Software; 2004. Available at http://lpsolve.sourceforge.net/5.5/. Last accessed Dec, 18 2009.

45. Klevens RM, Edwards JR, Chesley L. Richards J, et al. Estimating Health Care-Associated Infections and Deaths in U.S. Hospitals, 2002. *Public Health Reports* 2007; 122(2): 160-166. PMID: 17357358doi: 10.1177/003335490712200205

46. Zimlichman E, Henderson D, Tamir O, et al. Health care-associated infections: A meta-analysis of costs and financial impact on the us health care system. *JAMA Internal Medicine* 2013; 173(22): 2039-2046. doi: 10.1001/jamainternmed.2013.9763

47. Cooper BS, Stone SP, Kibbler CC, et al. Isolation measures in the hospital management of methicillin resistant Staphylococcus aureus (MRSA): systematic review of the literature. *BMJ* 2004; 329(7465): 533. doi: 10.1136/bmj.329.7465.533

48. Harris A, Pineles L, Belton B, et al. Universal glove and gown use and acquisition of antibiotic-resistant bacteria in the icu: A randomized trial. *JAMA* 2013; 310(15): 1571-1580. doi: 10.1001/jama.2013.277815

49. Widerstrom M, Monsen T, Karlsson C, Wistrom J. Molecular epidemiology of meticillin-resistant coagulase-negative staphylococci in a Swedish county hospital: evidence of intra- and interhospital clonal spread. *The Journal of Hospital Infection* 2006; 64(2): 177-183.

50. McAdam PR, Templeton KE, Edwards GF, et al. Molecular tracing of the emergence, adaptation, and transmission of hospital-associated methicillin-resistant Staphylococcus aureus. *Proceedings of the National Academy of Sciences* 2012; 109(23): 9107–9112. doi: 10.1073/pnas.1202869109

51. Ke W, Huang SS, Hudson LO, et al. Patient sharing and population genetic structure of methicillin-resistant Staphylococcus aureus. *Proceedings of the National Academy of Sciences* 2012; 109(17): 6763–6768. doi: 10.1073/pnas.1113578109

52. Roman RS, Smith J, Walker M, et al. Rapid geographic spread of a methicillin-resistant Staphylococcus aureus strain. *Clinical Infectious Diseases* 1997; 25(3): 698-705. doi: 10.1086/513758

53. Tansel O, Kuloglu F, Mutlu B, et al. A methicillin-resistant Staphylococcus aureus outbreak in a new University hospital due to a strain transferred with an infected patient from another city six months previously. *The new microbiologica* 2003; 26(2): 175âĂŤ180.

54. Svoboda T, Henry B, Shulman L, et al. Public health measures to control the spread of the Severe Acute Respiratory Syndrome during the outbreak in Toronto. *New England Journal of Medicine* 2004; 350(23): 2352-2361. PMID: 15175437doi: 10.1056/NEJMoa032111

55. Simmering JE, Polgreen LA, Campbell DR, Cavanaugh JE, Polgreen PM. Hospital transfer network structure as a risk factor for Clostridium difficile infection. *Infection Control & Hospital Epidemiology* 2015; 36(9): 1031âĂŞ1037. doi: 10.1017/ice.2015.130

56. Slayton R, Baggs J, McCormick K, Elligson K, Jernigan J. Association between healthcare facility connectedness and the incidence of Clostridium difficile infections, Washington and Oregon. *Open Forum Infectious Diseases* 2016; 3(suppl$_1$) : 840.doi : 10.1093/$ofid$/ofw194.47

57. Lee BY, McGlone SM, Wong KF, et al. Modeling the spread of methicillin-resistant Staphylococcus aureus (MRSA) outbreaks throughout the hospitals in Orange County, California. *Infection Control & Hospital Epidemiology* 2011; 32(06): 562–572.

58. Lesosky M, McGeer A, Simor A, Green K, Low DE, Raboud J. Effect of patterns of transferring patients among healthcare institutions on rates of nosocomial Methicillin-Resistant Staphylococcus aureus transmission: A Monte Carlo simulation. *Infection Control & Hospital Epidemiology* 2011; 32(2): 136âĂŞ147. doi: 10.1086/657945

59. Smith DL, Dushoff J, Perencevich EN, Harris AD, Levin SA. Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: Resistance is a regional problem. *Proceedings of the National Academy of Sciences* 2004; 101(10): 3709–3714. doi: 10.1073/pnas.0400456101

60. Smith DL, Levin SA, Laxminarayan R. Strategic interactions in multi-institutional epidemics of antibiotic resistance. *Proceedings of the National Academy of Sciences* 2005; 102(8): 3153–3158. doi: 10.1073/pnas.0409523102

61. Donker T, Wallinga J, Grundmann H. Patient Referral Patterns and the Spread of Hospital-Acquired Infections through National Health Care Networks. *PLOS Computational Biology* 2010; 6(3): 1-9. doi: 10.1371/journal.pcbi.1000715

62. Donker T, Wallinga J, Slack R, Grundmann H. Hospital Networks and the Dispersal of Hospital-Acquired Pathogens by Patient Transfer. *PLOS ONE* 2012; 7(4): 1-8. doi: 10.1371/journal.pone.0035002

63. Ciccolini M, Donker T, KÃűck R, et al. Infection prevention in a connected world: The case for a regional approach. *International Journal of Medical Microbiology* 2013; 303(6): 380 - 387. Special Issue Antibiotic Resistancedoi: https://doi.org/10.1016/j.ijmm.2013.02.003

64. Sewell DK, Simmering JE, Justice S, Pemmaraju SV, Segre AM, Polgreen PM. Estimating the Attributable Disease Burden and Effects of Inter-Hospital Patient Sharing on Clostridium difficile Infections. *Infection Control and Hospital Epidemiology* 2019. In press.

65. Marsden E, Torgerson CJ. Single group, pre- and post-test research designs: Some methodological concerns. *Oxford Review of Education* 2012; 38(5): 583-616. doi: 10.1080/03054985.2012.731208