Controlling nosocomial infection based on structure of hospital social networks

Taro Ueno [a], Naoki Masuda [b],*

[a] *Tokyo Metropolitan Hiroo General Hospital, 2-34-10 Ebisu, Shibuya, Tokyo 150-0013, Japan*
[b] *Graduate School of Information Science and Technology, The University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-8656, Japan*

ABSTRACT

Nosocomial infection (i.e. infection in healthcare facilities) raises a serious public health problem, as implied by the existence of pathogens characteristic to healthcare facilities such as methicillin-resistant *Staphylococcus aureus* and hospital-mediated outbreaks of influenza and severe acute respiratory syndrome. For general communities, epidemic modeling based on social networks is being recognized as a useful tool. However, disease propagation may occur in a healthcare facility in a manner different from that in a urban community setting due to different network architecture. We simulate stochastic susceptible-infected-recovered dynamics on social networks, which are based on observations in a hospital in Tokyo, to explore effective containment strategies against nosocomial infection. The observed social networks in the hospital have hierarchical and modular structure in which dense substructure such as departments, wards, and rooms, are globally but only loosely connected, and do not reveal extremely right-skewed distributions of the number of contacts per individual. We show that healthcare workers, particularly medical doctors, are main vectors (i.e. transmitters) of diseases on these networks. Intervention methods that restrict interaction between medical doctors and their visits to different wards shrink the final epidemic size more than intervention methods that directly protect patients, such as isolating patients in single rooms. By the same token, vaccinating doctors with priority rather than patients or nurses is more effective. Finally, vaccinating individuals with large betweenness centrality (frequency of mediating connection between pairs of individuals along the shortest paths) is superior to vaccinating ones with large connectedness to others or randomly chosen individuals, which was suggested by previous model studies.

© 2008 Elsevier Ltd. Open access under CC BY-NC-ND license.

1. Introduction

Nosocomial infection, that is, infection in healthcare facilities, is health-threatening for hospitalized patients and caregivers (Gastmeier et al., 2005; Grundmann and Hellriegel, 2006). Pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are mainly nosocomial in the sense that the majority of cases are hospital-related (Salgado et al., 2003; Cooper et al., 2004). In addition, as observed in recent cases of influenza (CDR weekly, 2005) and severe acute respiratory syndrome (SARS) (Ho et al., 2003; Leung et al., 2004; Svoboda et al., 2004), nosocomial infection serves as an initiator or a booster of epidemic outbreaks at urban community and world-wide levels. In accordance, mathematical models specialized in nosocomial infections and their

controls have been developed, with intensive emphases on antibiotic-resistant bacteria (Lipsitch et al., 2000; Pelupessy et al., 2002; Forrester and Pettitt, 2005; Bootsma et al., 2006; Boldin et al., 2007) and intensive care units (Pelupessy et al., 2002; Perencevich et al., 2004; Forrester and Pettitt, 2005; Boldin et al., 2007). Quantitative statistical models for nosocomial infection have also been reported (Cooper and Lipsitch, 2004; Forrester and Pettitt, 2005; Forrester et al., 2007).

In this work we examine the possibility of using the information on social networks in healthcare facilities for developing containment protocols. There have been many modeling reports on disease spreading on complex social networks (Meyers et al., 2003, 2005; Christley et al., 2005; Keeling and Eames, 2005; Pourbohloul et al., 2005; Watts et al., 2005; Colizza et al., 2006; Green et al., 2006; Riley, 2007; Volz and Meyers, 2007). A central theoretical finding is that hubs, namely, those who have contacts to relatively many others, communicate and enhance disease transmission. Diseases spread to a great extent with larger probability on heterogeneous networks

* Corresponding author. Tel.: +81 3 3812 2111.
  E-mail address: masuda@mist.i.u-tokyo.ac.jp (N. Masuda).

such as scale-free networks in which the number of contacts that each individual maintains is highly heterogeneous (Hethcote and Yorke, 1984; Anderson et al., 1986; Albert et al., 2000; Pastor-Satorras and Vespignani, 2001). Such heterogeneous networks are operative in sexually transmitted diseases (Liljeros et al., 2001) and computer viruses (Pastor-Satorras and Vespignani, 2001).

However, this and other findings in network epidemiology so far do not seem to have a sufficient descriptive power for nosocomial infections for two main reasons. First, social networks of healthcare facilities may be structured differently from networks of urban communities or the whole world. In terms of size, a hospital is typically much smaller than an urban community. In terms of microscopic structure, contact patterns in a hospital are regulated by hierarchy defined by departments, wards, and rooms. To our knowledge, efficient containment strategies for social networks with such modular structure have not been established. Second, a healthcare facility is composed of individuals of distinct roles, such as patients, visitors, and healthcare workers. Healthcare workers can be subdivided into different classes, such as nurses and medical doctors. Susceptibility, mortality, infectiousness, and many other factors that affect how diseases spread depend on the type of individuals. For example, junior doctors may visit more wards than nurses do, possibly carrying pathogens from ward to ward (CDR weekly, 2005). Patients may be less active but likely have larger case fatality (i.e. fraction of death among infected individuals) than healthcare workers (Leung et al., 2004; Forrester and Pettitt, 2005). In urban community social networks, the role of different types of individuals in disease propagation may not be so clear-cut.

In spite of seminal modeling work of nosocomial infection based on network analysis (Meyers et al., 2003; Liljeros et al., 2007), how diseases spread in potentially hierarchical networks of healthcare facilities composed of individuals of different classes is not sufficiently understood. In this work, we model nosocomial infection in social networks based on observations of contact frequency in a hospital in Tokyo. We simulate stochastic susceptible-infected-recovered (SIR) epidemic dynamics on these networks and evaluate effectiveness of intervention and vaccination protocols. We show that medical doctors that move between wards, but not patients or nurses each of whom is attached to a single ward, are principal vectors (i.e. transmitters) of pathogens. In accordance, we show that reallocating patients to medical doctors reduces epidemic spreading to a larger extent than preparing single rooms to isolate patients. We also show that the vaccination protocols that principally target healthcare workers, particularly medical doctors, located in key positions determined by network analysis are more effective than those focusing on patients or on simply most connected individuals.

2. Methods

2.1. Data

We construct two social networks in a community hospital located in Tokyo, based on medical records collected at two instants, namely, a day in a weekend in September 2007 and a weekday in November 2007. The use of the data in this study was approved by the Hospital Ethics Committee. These two datasets are different mainly in that more nurses work on the weekday. Another minor difference is that some resident doctors occupy very different parts of the two networks because they change the department every month. We use these two networks as two independent snapshots and do not consider longitudinal factors caused by, for example, shift work, admission of patients, discharge of patients, and seasonality.

This hospital is a 482 bed tertiary referral teaching hospital, with 16 wards and 129 rooms. Patients occupy either shared or single rooms. There are relatively few single rooms (37 rooms, or 7.68% of the total beds). A ward has 8.06 rooms on average (max 10, min 4) and usually hosts patients from different departments. A department typically has patients scattered in different wards. Therefore, as nurses work in single wards, they are likely to attend patients from a number of departments. On average, about five nurses work in a ward (5.88 on the weekday and 4.31 on the weekend).

As schematically shown in Fig. 1a, one line of the medical record contains the identity of a patient accompanied by those of a nurse and medical doctors in responsibility. A patient is assigned a single nurse and is examined by at least one doctor. Usually, a couple of doctors form a team so that a patient is examined by multiple doctors in the team. A typical team consists of two or three doctors of different ranks. A patient is also examined by multiple doctors when the patient registers at multiple departments, but such an occasion is rare (none on the weekday and just one patient on the weekend). As a note, resident doctors (25 among 123 doctors on the weekday and 29 among 123 on the weekend) often belong to more than one department, because they may retain their previous patients in addition to gaining new ones every month in different departments. All the other medical doctors are specialists and belong to only one department. All doctors, including residents, typically visit a number of wards over which their patients are scattered, the maximum number of wards visited by a single doctor for these data being five.

The edges of the networks, which represent social contacts between pairs of individuals, are defined as follows. We denote patient, nurse, and medical doctor, by Pt, Ns, and Dr, respectively. The Pt–Ns, Pt–Dr, Ns–Dr, and Dr–Dr edges (for example, a Pt–Ns edge is an edge between a patient and a nurse) are determined based on the medical record (Fig. 1a). All pairs of individuals in the same line of the medical record are connected to each other. Accordingly doctors in the same team are connected to each other. Additionally, a patient is connected to all the other patients in the same room (Fig. 1b). This is the single source of Pt–Pt edges. Similarly, a nurse is connected to all the other nurses working in the same ward to form Ns–Ns edges (Fig. 1c). We neglect other
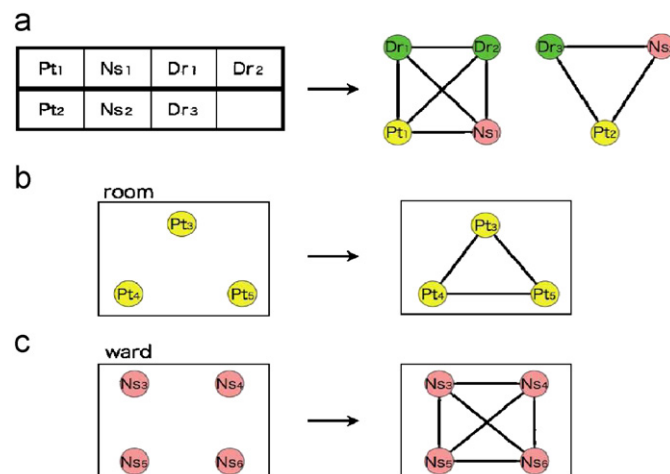

Fig. 1. Construction of (a) Pt–Ns, Pt–Dr, Ns–Dr, Dr–Dr edges, (b) Pt–Pt edges, and (c) Ns–Ns edges.

possible contacts, such as casual friendships that do not appear in the medical record.

The edges of the networks are assumed to be fixed over time, undirected, and unweighted, so that disease transmission occurs bidirectionally with the same strength. Even if a particular Ns–Dr pair or Dr–Dr pair may appear in multiple lines in the medical record, we do not double count this relation because double counting would lead to excessive weighting of Ns–Dr and Dr–Dr edges. For example, the two doctors in the same team would be connected by five edges if this team examines five patients.

2.2. Epidemic dynamics

We simulate the stochastic SIR model on the static observed networks. Each individual takes one of the three states represented by S (susceptible), I (infected), and R (recovered or dead). Initially, a prescribed index individual is infected, and all the other individuals are susceptible. Any susceptible individual is subject to contagion when that individual has an infected neighbor in the social network. We assume that the infection rate is frequency-dependent, that is, proportional to the number of edges that an individual has (Lloyd-Smith et al., 2004). We denote the unitary infection rate by λ. Assuming that the possibility of infection events depends the present, but not past, configuration of S, I, and R on the network, a susceptible is infected by each infected individual in the neighborhood with probability $1 - \exp(-\lambda \Delta t)$ in time Δt. Note that, when Δt is small, the probability that a susceptible becomes infected is approximated by $\lambda \Delta t$ times the number of infected neighbors. Equivalently, an infected individual infects each of its susceptible neighbors with probability $\lambda \Delta t$. The infection rate λ is common for different edges and individuals unless otherwise stated.

An infected individual continues infecting neighboring individuals until recovery occurs (and the individual enters state R) after a random time. The transition rate from state I to state R is set equal to unity for normalization, so that an infected individual transits to state R with probability $1 - \exp(-\Delta t)$ for time Δt. When Δt is small, this probability is approximated by Δt, and one recovery event occurs per unit time on average. This event happens independently of the neighbors' states. Individuals in state R are assumed to be either immune or dead. We consider both interpretations in the following analyses. In either case, they cannot infect, or be infected by, other individuals.

Because the transition rate from state I to state R is normalized to unity, the infection rate λ controls the strength of a disease. When λ is large enough, with high probability, the number of the infected grows progressively in the early stages and the number of the susceptible decreases accordingly. After some delay, state-R individuals begin to appear, and the number of the infected individuals begins to decline. Finally the population is composed of only state S and R individuals, which halts the dynamics. We perform each numerical simulation until this situation is reached. Because the SIR dynamics are stochastic, we take averages over trials for calculating the mean statistics. For each configuration, the average is taken over 100 trials for each index case and over all the individuals as index cases.

3. Results

3.1. Network structure

The observed weekday network contains 605 individuals (388 patients, 94 nurses, 123 medical doctors) and 3046 edges (Table 1).

Table 1
The number of individuals and each type of edges for the original weekday network and the networks after intervention

Type of edge	Original	1	1 (dup)	2	2 (dup)	3
Total	3046	2823	3016	2717	3004	2382
Pt–Pt	664	664	664	664	664	0
Pt–Ns	388	388	388	388	388	388
Pt–Dr	927	911	927	857	927	927
Ns–Ns	245	245	245	245	245	245
Ns–Dr	661	488	661	444	661	661
Dr–Dr	161	131	131	119	119	161

Type of individuals	Number
Total	605
Pt	388
Ns	94
Dr	123

The characteristic path length of the network, which is defined as the mean shortest path length between all the pairs of individuals, $L = 4.84$. The clustering coefficient, which counts the abundance of local connectivity by the density of triangles normalized between 0 and 1, $C = 0.534$. A relatively small value of L and a large value of C of this network implies the small-world property (Watts and Strogatz, 1998). Although the hospital network has a considerably smaller L than spatially structured networks such as the square lattice (a regular two-dimensional network), it is not perfectly mixed. If we rewire the edges randomly with the degree (number of edges that an individual has) of each individual fixed, L even decreases to 2.97 and clustering is lost ($C = 0.0251$). This behavior of L and C upon random rewiring of edges is similar to that for the Watts–Strogatz network model (Watts and Strogatz, 1998). The path length L of the original network is larger than the randomized network because of some localization of individuals. First, patients are connected to each other within one room only. Therefore, intraroom edges are dense relative to interroom edges. Second, each patient and nurse is attached to a single ward and only connected to patients and nurses inside that ward; only medical doctors link different wards. Therefore, intraward edges are dense relative to interward edges. Third, doctors are localized in the sense that doctors visit only the wards with patients from their own department and that doctors in the same team have correlated contact patterns and mutual connections. The entire network is composed of relatively dense subnetworks (also called communities or network modules in network literature, e.g. Girvan and Newman, 2002; Palla et al., 2005) that are loosely interlinked in a hierarchical manner.

The degree distribution is shown in Fig. 2 separately for each class. Unlike social networks underlying sexually transmitted diseases (Hethcote and Yorke, 1984; Anderson et al., 1986; Liljeros et al., 2001) and computer viruses (Pastor-Satorras and Vespignani, 2001), our hospital social networks do not have right-skewed degree distributions. A skewed degree distribution would imply that a fraction of caregivers with very large degrees are extremely busy, whereas others are not.

3.2. Basic epidemic dynamics

The final epidemic size is defined to be the sum of the state R individuals regardless of the class (Pr, Ns, and Dr) at the end of the epidemic dynamics, normalized between 0 and 1.

The average final size calculated numerically is shown in Fig. 3a (solid line) for the weekday network. The final size increases as the infection rate λ increases, taking off the zero
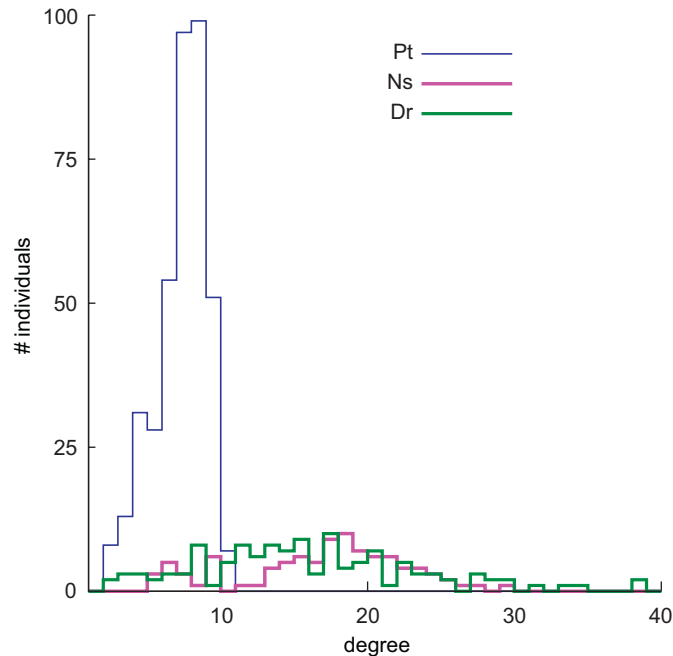

Fig. 2. Degree distributions of the weekday network for different classes of individuals.

floor around $\lambda = 0.13$, for which the basic reproduction number, which is the expected number of secondary cases originating from an index case, crosses unity. Beyond this point, a large-scale (i.e. major) epidemic may occur.

The distribution of the final size is shown in Fig. 3b. The average of the distribution shown as each vertical cross section, i.e. for each value of λ, corresponds to the solid line in Fig. 3a. Above a threshold infection rate, the distribution has two masses. One thin mass is concentrated around zero and indicates that, despite a large infection rate, the epidemic can quickly decline to extinction owing to demographic stochasticity of state I individuals (i.e. minor epidemic). The other mass is centered around a positive value of the final size and corresponds to the major epidemic. Precisely speaking, the major epidemic consists of two peaks. This is because one ward, which is devoted to the psychiatry department, has 42 (of 605) individuals and is connected to the rest of the network via only two junior doctors. These doctors examine patients from departments to which they previously belonged, in addition to patients from the psychiatry department. Suppose that the disease starts from the index case in this ward. Disease must pass through the narrow channel composed of the two doctors to spread to the rest of the population. This event occurs with a somewhat low probability even for very large infection rates. This causes the lower peak of the upper mass around 0.9 in Fig. 3b, which is eminent for $\lambda \geqslant 0.8$. We confirmed that a two-mass distribution, possibly with subdivisions of each mass reflecting modular structure of the network, underlies each of the following numerical results. In addition, whereas an epidemic whose final size is near the mean value rarely occurs because of the two-mass distribution shown in Fig. 3b, a larger mean final size indicates a larger probability of major epidemic. Therefore
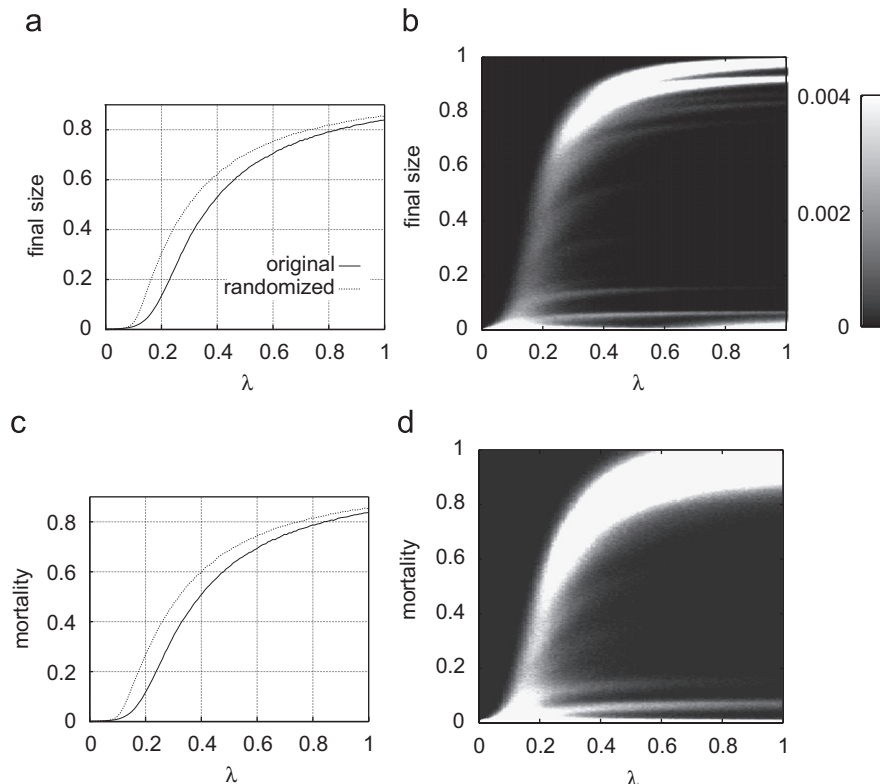

Fig. 3. Disease spread in the weekday network. (a) Final size for the original network (solid lines) and the randomized network (dashed lines). (b) Distribution of the final size. (c) Fraction of mortality. (d) Distribution of the fraction of mortality. A brighter point in (b) and (d) corresponds to a larger probability density.

we will show only the mean values of the final size in later figures.

Both for nosocomial pathogens such as MRSA (Forrester and Pettitt, 2005) and other pathogens such as SARS (Leung et al., 2004), the case fatality of hospitalized patients is much larger than that of healthcare workers. The final sizes shown in Fig. 3a and b represent incidences, that is, infection events. Frequency of observing severe manifestations or deaths needs to be discussed separately. To highlight differential mortalities between healthcare workers and patients (Leung et al., 2004), we assume that only patients, not nurses or medical doctors, always die after being infected for some time (see Discussion for justification). The nurses and doctors in state R are assumed to be cured after being infected. These individuals are counted for the final size but not for the final fraction of mortality. Consequently, the final fraction of mortality is defined to be the final fraction of state R among the patients only. The fraction of mortality and its distribution, shown in Fig. 3c and d, respectively, change little from those for the final size.

The randomized network yields a larger final size and larger mortality (dashed lines in Fig. 3a and c) than the original network. This is because the randomized network has a small L so that, on average, individuals are linked by a short distance compared to the case of the original network.

The weekend network has characteristics similar to the weekday network, with 521 individuals (329 patients, 69 nurses, 123 medical doctors), 2364 edges, $L = 4.39$, and $C = 0.535$ (Table A1). The randomized network has $L = 3.015$ and $C = 0.0286$. The degree distribution and the SIR results for the original and randomized networks are shown in Figs. A1 and A2, respectively. The final size, the mortality, and their distributions are shown in Fig. A2. These results are qualitatively similar to those for the weekday network. The following results for the intervention and vaccination protocols are also qualitatively the same for the weekday and the weekend network. Therefore, we explain the weekday results in the main text and relegate the weekend results to Appendix A.

3.3. Interventions

We examine the effects of three intervention methods on the suppression of epidemic spreading. We design these intervention methods so that they may be practiced in real situations before a potential epidemic happens. The cost of implementation is presumably the smallest for method 1 and the largest for method 3.

3.3.1. Intervention 1: reassigning patients to medical doctors

Medical doctors are likely to be efficient vectors of pathogens because they examine their patients scattered in multiple wards. In contrast, nurses and patients are constrained to one ward. In intervention 1, we reduce visits of doctors to different wards by reassigning patients to different doctors. Originally a couple of doctors in the same department formed a team to examine a set of patients, who were potentially scattered across different wards. Under the intervention, we reassign the patients without destroying the team structure; we will relax this condition in the next intervention method. Suppose that both teams t_1 and t_2 examine a patient in ward w_1 and another patient in ward w_2. In the example shown in Fig. 4a, teams t_1 and t_2 trade one of their patients. Then team t_1 examines two patients in ward w_1 and team t_2 examines two patients in ward w_2, thus allowing each team to visit just one ward. We apply this operation wherever possible so that we constrain each team of doctors
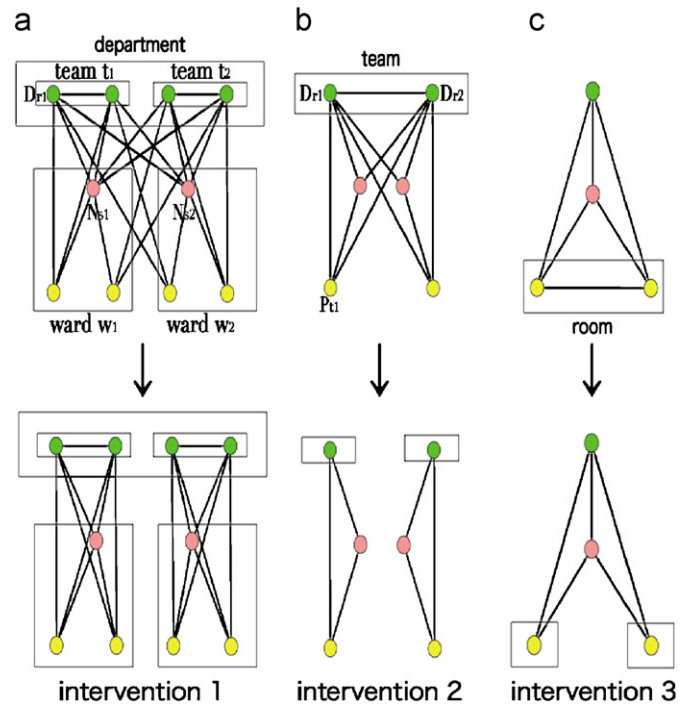

Fig. 4. Schematics of three intervention methods.

to as few wards as possible, often enabling confinement to just one ward.

By intervention 1, the numbers of Pt–Pt edges, Pt–Ns edges, and Ns–Ns edges are preserved (Table 1). The number of Pt–Dr edges slightly decreases because some patients are reassigned with a team of a smaller number of doctors after intervention than before intervention. The number of Ns–Dr edges decreases because a doctor visits a smaller number of wards after the intervention. Then, for example, doctor Dr_1 in Fig. 4a tends to spend more time with nurse Ns_1, whereas this doctor is no longer connected to Ns_2. The number of Dr–Dr edges decreases because, in some departments, some of the teams are dismissed after intervention 1. In such departments, some doctors belong to multiple teams before intervention and to a smaller number of teams after intervention. The edges in the original network that link two doctors sharing dismissed team only are absent in the post-intervention network. Due to the reduction in doctor-related edges, the total number of edges decreases from 3046 to 2827.

The numerical results for the final size and the mortality after intervention 1 are shown in Fig. 5a and b, respectively (lines with legend '1'). We find considerable decreases in both quantities compared to the case of the original network. Note that this intervention does not require introduction of additional infrastructure.

One may argue that the suppression of epidemics comes from a significant decrease in the number of Ns–Dr edges. To exclude this possibility, we examine the network in which the Pt–Dr and Ns–Dr edges are duplicated through the intervention. With this modification, doctor Dr_1 and nurse Ns_1 in Fig. 4a, for example, is connected by two edges. Equivalently, we increase the transmission rate of this single edge twofold to account for the doubled contact rate between them, which comes from the fact that Dr_1 and Ns_1 examine twice patients together (two patients after the intervention versus one patient before the intervention). The edge duplication is also done for a Pt–Dr edge whenever
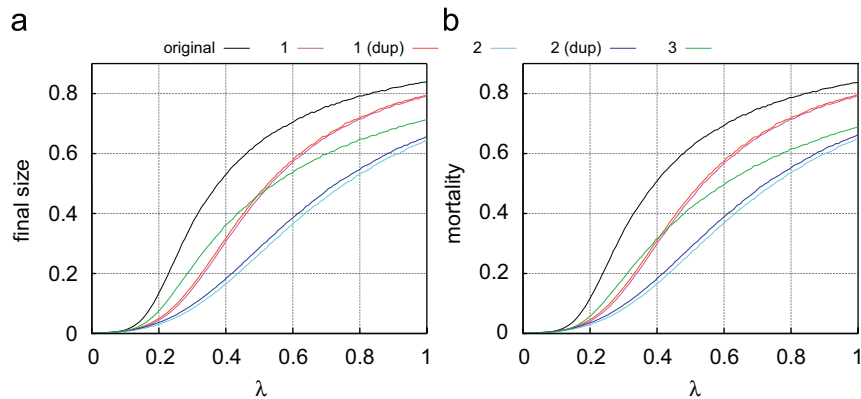
Fig. 5. Effects of different intervention protocols for the weekday network. (a) Final size and (b) fraction of mortality. Different lines correspond to the original observed network ('original'), networks after intervention 1 ('1'), intervention 1 with edge duplication ('1 (dup)'), intervention 2 ('2'), intervention 2 with edge duplication ('2 (dup)'), and intervention 3 ('3').

the number of doctors that examine the patient on this edge decreases as a result of intervention. Consequently, the number of Pt–Dr edges and that of Ns–Dr edges return to those of the original network. This implies that the quality of the medical service that we measure by the number of Pt–Ns and Pt–Dr edges does not degrade due to the intervention. The number of edges in total after this modified intervention 1 is 3016, which is close to the number for the original network (i.e. 3046 edges; also see Table 1).

The numerical results shown in Fig. 5a and b (lines with legend '1 (dup)') indicate that this modification little spoils the effectiveness of intervention 1. A large portion of the reduced epidemics is owing to the reassignment of patients, but not to cutting edges.

3.3.2. Intervention 2: dissolving teams

Next we investigate a more costly intervention method. The team structure of medical doctors generally enables them to reach better medical solutions through discussion and knowledge accumulation in the team. It also helps training junior doctors. However, team structures provide channels for rapid disease transmission among wards, with doctors serving as vectors. Another related negative effect of the team structure is that patients and nurses are subject to extra infection events because they are connected to multiple doctors.

We dissolve the team in intervention 2. In the schematic example shown in Fig. 4b, each patient is examined by both doctors in the team before intervention. By intervention 2, we assign each patient to one, but not two, of the doctors. For example, Pt_1 was examined by Dr_1 and Dr_2 before the intervention, but only by Dr_1 after the intervention. In practice, this intervention may be discouraged if it results in resident or junior doctors examining patients alone. Therefore, we decompose the teams as much as possible under the condition that each resident doctor remains teamed with a senior doctor. The numbers of Pt–Pt, Pt–Ns, and Ns–Ns edges are preserved through the intervention. The total number of edges drops from 3046 to 2717 owing to the reduction in doctor-associated edges, as summarized in Table 1.

The final size and the mortality are shown in Fig. 5 (lines with legend '2'). Intervention 2 is more effective than intervention 1.

To calibrate the effect of the decrease in the number of edges, we do additional numerical simulations. As an example, suppose that Pt_1 in Fig. 4b is examined by Dr_1 for twice as long after the intervention than in the pre-intervention situation

where Pt_1 is examined by two doctors. Accordingly, we duplicate the edge between Pt_1 and Dr_1. In addition, we compensate the contact rate, or the number of edges, between nurses and doctors by duplicating the corresponding Ns–Dr edges, as in intervention 1. Taking the edge duplication into account, the numbers of Pt–Dr and Ns–Dr edges, as well as those of Pt–Pt, Pt–Ns, and Ns–Ns edges, are preserved. A byproduct of this modification is that the service quality assessed by the amount of the Pt–Ns and Pt–Dr edges is restored. The total number of edges after modified intervention 2 is 3004 (see Table 1 for the number of each type of edges), which is close to 3046, the number for the original network. The persisting reduction in the number of edges comes from that of Dr–Dr edges. As shown in Fig. 5 (lines with legend '2 (dup)'), this modification has little influence on the effectiveness of intervention 2. As in intervention 1, the reduced mortality is ascribed to the intentional changes in network structure, but not to simply cutting edges.

3.3.3. Intervention 3: introduction of single rooms

In intervention 3, we attempt to prevent disease spreading among patients by making all the rooms single, as suggested by previous literature (Cooper et al., 2004). Accordingly, we isolate the patients by removing all the Pt–Pt edges, with the other types of edges and hence the service quality kept intact. The schematic of this procedure is shown in Fig. 4c. Then, the total number of edges decreases from 3046 to 2382 (Table 1).

The final size and the mortality results shown in Fig. 5 (lines with legend '3') suggest that intervention 3 is not as effective as interventions 1 and 2, except when the infection rate is large. Even if we focus on the patient cases only, as shown in Fig. 5b, it is more effective to reduce Dr-related edges (interventions 1 and 2), than to reduce Pt–Pt edges (intervention 3).

Note that the number of removed edges is much larger ($= \frac{642}{3046}$) than for intervention 1 ($= \frac{223}{3046}$) and intervention 2 ($= \frac{332}{3046}$). Generally speaking, cutting down more edges typically results in a reduced epidemic size. However, this pattern does not appear for the present network. This is because patients are largely confined to their rooms and Pt–Pt edges do not play an important role in epidemics on a large scale. For a very large infection rate, intervention 3 is better than intervention 1. However, the final size and the mortality for intervention 3 are still larger than those for intervention 2. For an extremely large infection rate for which more than two-thirds of the population becomes infected, intervention 3 is more efficient at control than intervention 2. Our claim that introducing single rooms may be ineffective is
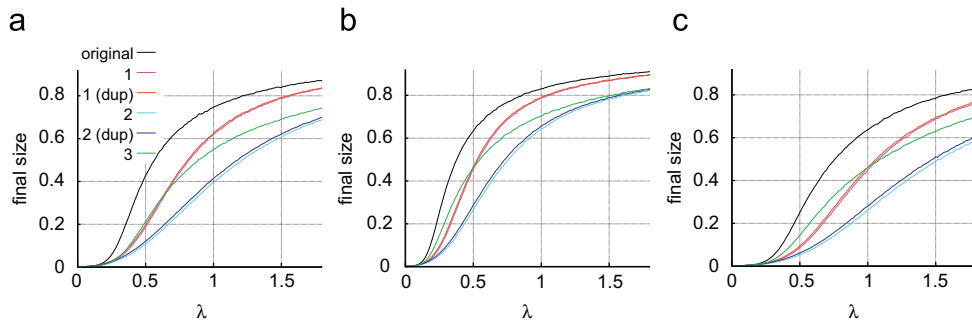
Fig. 6. Sensitivity analysis. The final size is compared for different intervention protocols (see legends of Fig. 5 for details). The infection rate is halved for (a) susceptible nurses and doctors. (b) Infected patients, and (c) infected nurses and doctors.
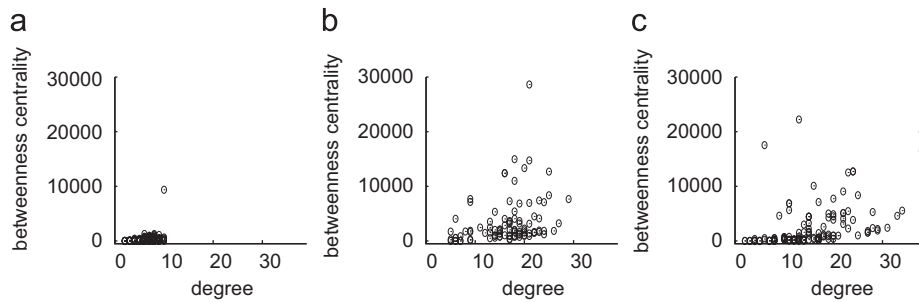

Fig. 7. Betweenness centrality plotted against degree for the weekday network for (a) patients, (b) nurses, and (c) doctors.

consistent with an observation analysis (Cepeda et al., 2005) and a modeling study (Bootsma et al., 2006) of MRSA.

3.3.4. Sensitivity analysis

To show the generality of the intervention results, we perform three sets of numerical simulations in which we change infection rates of individuals differently. First, the rate at which each susceptible nurse and doctor is infected is halved, representing the biological possibility that patients are more likely to be infected than healthcare workers. Second, the rate at which each infected patient infects susceptible neighbors is halved, representing the possibility that healthcare workers have higher infection rates than patients. Third, the rate at which each infected nurse and doctor infects susceptible neighbors is halved, corresponding to the opposite of the second variation.

The effects of different intervention protocols on the final size are compared in Fig. 6 for the three variations described above. The mortality results are quantitatively very close to the final size results in Fig. 6 (not shown). In all the three variations, interventions 1 and 2 (particularly, intervention 2) are more efficient than intervention 3 at low to intermediate infection rates, which agrees with the results for the original SIR model shown in Fig. 5.

3.4. Vaccination

We explore efficient vaccination strategies under the condition that vaccines are available only to a proportion of individuals. The simplest strategy would be to randomly pick individuals for vaccination. However, a number of studies suggest that random vaccination is inferior to a contact-based vaccination strategy in which those with largest degrees are vaccinated

(Albert et al., 2000; Cohen et al., 2003; Pourbohloul et al., 2005; Bansal et al., 2006). In theory, a degree-based vaccination strategy is effective for well-mixed heterogeneous networks in which individuals are connected at random. However, as shown in Section 3.1, the observed hospital networks are not entirely mixed in this sense, but instead have a modular, hierarchical structure.

We compare the degree-based vaccination strategy with other strategies. The degree is a local measure of centrality by which individuals connected to many others are regarded to be important. Many centrality measures have been proposed (e.g. Junker et al., 2006). In a well-mixed network, the degree is correlated well with most other centrality measures so that hubs are central in most senses. However, the observed hospital network is not entirely well-mixed. As an example, we consider the betweenness centrality, which is a count of how often an individual mediates the communication between arbitrarily chosen pairs of individuals along the shortest paths (Freeman, 1979). Fig. 7, which compares the degree and the betweenness centrality of each individual in the hospital, indicates that the most connected individuals are not necessarily those with the greatest betweenness centrality values.

For a fixed centrality measure, we vaccinate the 20 individuals with the largest centrality values, thus effectively remove them from the network. Then we run the SIR dynamics on the reduced network. The drops in the final size and the mortality size relative to those for the original network are interpreted as the effectiveness of a vaccination method.

The final size (Fig. 8a) and the mortality (Fig. 8b) with each of four vaccination protocols are compared to those for the original network. Degree-based vaccination is more effective at reducing epidemics than random vaccination (compare lines with legend 'random' and ones with legend 'degree' in Fig. 8), which agrees with the results in previous literature (Albert et al., 2000;
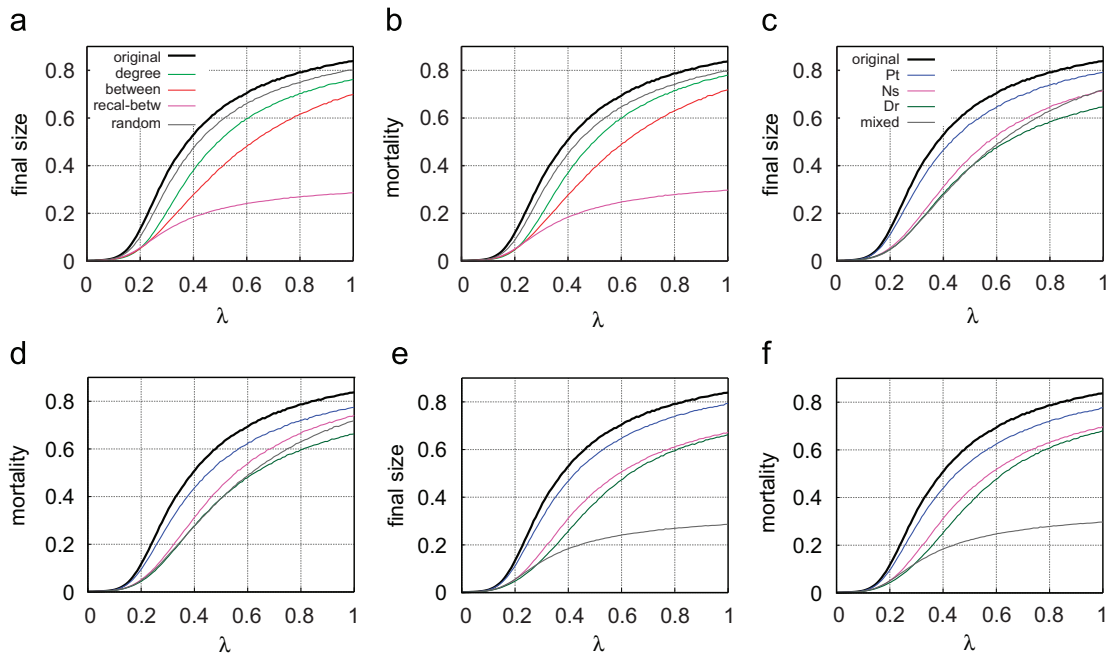
Fig. 8. Effects of vaccination strategies for the weekday network. (a) Final size and (b) mortality for different centrality-based and random vaccination strategies. Different lines correspond to the original observed network ('original'), degree-based vaccination ('degree'), betweenness-based vaccination ('between'), vaccination based on the recalculated betweenness centrality ('recal-betw'), and random vaccination ('random'). (c) Final size and (d) mortality for the vaccination strategy based on the betweenness centrality and the class of individuals. (e) Final size and (f) mortality for the vaccination strategy based on the recalculated betweenness centrality and the class of individuals. In (c)–(f), different lines correspond to the original network ('original'), Pt-first protocol ('Pt'), Ns-first protocol ('Ns'), Dr-first protocol ('Dr'), and class-mixed protocol ('mixed').

Cohen et al., 2003; Pourbohloul et al., 2005; Bansal et al., 2006). The degree-based vaccination is superceded by the betweenness-based vaccination for a wide range of λ, agreeing with the previous modeling work by Holme et al. (2002). The betweenness-based vaccination is effective because interward communication is inhibited after vaccination of key individuals. These key individuals are mostly medical doctors and sometimes nurses. In our simulations, the two doctors who connect the nearly isolated ward to the remainder of the network, whom we mentioned in Section 3.2, have the largest and the third largest betweenness centrality values. These doctors are actually vaccinated in the betweenness-based protocol. A disease does not enter a subnetwork if the entire network is fragmented after removing such key individuals. Even if the network is not fragmented after vaccination, a chain of transmission has to make detours, which makes disease spreading less likely. This is presumably because important shortcuts owned by central individuals have been cut out.

If we recalculate the betweenness centrality every time after removing the most central individual, the network generally falls apart in an earlier stage (Girvan and Newman, 2002; Holme et al., 2002). By doing so, epidemic spreads are more suppressed (Fig. 8a and b, lines with legend 'recal-betw'). The improvement is eminent for a large infection rate for which the disease tends to spread over many wards, infecting more than half the individuals in the hospital (λ around 0.8 and beyond). However, the final size and the mortality for nearly threshold infection rates (λ around 0.2) are slightly increased compared to the standard betweenness-based vaccination.

Our vaccination protocols up to this point do not take into account whether vaccinated individuals are patients, nurses, or medical doctors. We compare these class-mixed protocols to ones in which central individuals of a specific class are vaccinated with priority. For example, we vaccinate 20 doctors with the largest centrality values (doctor-first vaccination).

Based on the betweenness centrality, the final size and the mortality for patient-first, nurse-first, doctor-first, and class-mixed vaccination protocols are shown in Fig. 8c and d. The corresponding results based on the recalculated betweenness centrality are shown in Fig. 8e and f. For both centrality measures, the nurse-first strategy is less effective than the class-mixed and the doctor-first strategies. This is because, even though some nurses have large centrality values (Fig. 7b) comparable to those of the most central doctors (Fig. 7c), vaccinating nurses does not lead to dissociation of different wards; only doctors connect wards. The patient-first strategy is the least effective at reducing both the final size (Fig. 8c and e) and the mortality (Fig. 8d and f), because the patients have low centrality values irrespective of centrality measure (Fig. 7a). The doctor-first strategy is more effective than class-mixed strategy for the non-recalculated betweenness centrality (Fig. 8c and d) and vice versa for the recalculated betweenness centrality (Fig. 8e and f). The doctor-first strategy is better for both the non-recalculated and recalculated betweenness centrality for the weekend data (Fig. A4c–f).

We have also examined the vaccination protocols based on other centrality measures. For each of the centrality measures examined (closeness centrality, eigenvector centrality, power centrality, information centrality, and random-walk centrality; see Junker et al., 2006, for a list of centrality measures), the overall tendency that the class-mixed and doctor-first vaccinations are superior to the nurse-first vaccination, which supercedes the patient-first vaccination, is reproduced (not shown). Betweenness-type centrality measures such as the random-walk centrality turn out to be more effective at reducing epidemics than others. Whether the class-mixed strategy is superior to the doctor-based strategy depends on the centrality measure and whether the weekday network or the weekend network is used.

4. Discussion

We have investigated the effects of intervention and vaccination strategies using numerical simulations of the SIR model on hospital social networks. Both the intervention and vaccination results suggest that medical doctors that link different wards are main spreaders of nosocomial pathogens. To rewire the Pt–Dr relationship (interventions 1 and 2; particularly, intervention 2) is more efficient than suppressing Pt–Pt communication (intervention 3). Note that, in spite of the relative ineffectiveness of intervention 3, it involves construction of single rooms, which presumably costs more than interventions 1 and 2, and may result in reduction in the hospital admission capacity. Vaccinating doctors first suppresses epidemics more than vaccinating patients or nurses first. Importantly, doctor-centered containment strategies are more effective than patient-centered ones at reducing not only the final size of the entire population but also that of the patients.

We have found that the observed social networks do not have extremely right-skewed distributions of the degree, which differs from many other disease-related networks that have scale-free degree distributions (e.g. Albert et al., 2000; Liljeros et al., 2001). Instead, our observed networks in the hospital have modular and hierarchical structure regulated by wards, rooms, teams of medical doctors, and departments. Different modules are bridged by healthcare workers, especially by medical doctors. Therefore, the common result that scale-free networks boost epidemics owing to hubs, which hold for well-mixed networks with right-skewed degree distributions (Hethcote and Yorke, 1984; Anderson et al., 1986; Albert et al., 2000; Pastor-Satorras and Vespignani, 2001; Meyers et al., 2003, 2005; Christley et al., 2005), seems to be rather irrelevant to the current situation, as has been pointed out for other situations (Holme et al., 2002; Watts et al., 2005; Green et al., 2006; Ichinomiya, 2007). For our networks, we have shown that the vaccination protocols based on the betweenness centrality, which target individuals that tend to maintain shortcuts, are more effective than that based on the degree. The network structure identified in this work may serve as a basis for network-based quantification studies.

Healthcare workers have been suggested to be primary vectors and spreaders because they visit different wards (Elder et al., 1996; Carman et al., 2000; Meyers et al., 2003; Ho et al., 2003; CDR weekly, 2005; Burls et al., 2006). Therefore, vaccinating healthcare workers may be more effective than vaccinating patients in preventing nosocomial infection (Carman et al., 2000; Meyers et al., 2003). These results are consistent with ours. We have further distinguished roles of different classes of healthcare workers, namely, medical doctors and nurses, which was ignored in an observation study of nosocomial infection in which only patients were considered (Liljeros et al., 2007). We also examined the effects of individuality in terms of their position in the networks. We suggest that healthcare workers, doctors in particular, with large betweenness centrality values are of high mobidity in nosocomial infection. Because the betweenness centrality is an ad hoc measure for our purpose, there may be alternative measures more directly related to mobidity of individuals.

An implicit assumption underlying the vaccination strategies based on the betweenness and most other centrality measures is that the information on the global network structure is available. This assumption is not justified for urban community infections where the number of individuals involved is large and exhaustive contact tracing is infeasible. In this situation, a powerful vaccination strategy based on only the local information is ring vaccination in which vaccinations are provided along chains of contacts reconstructed by querying friends' names (Ferguson et al., 2001; Cohen et al., 2003; Pourbohloul et al., 2005). An alternative strategy is to abandon heterogeneous contact rates at the level of individuals and employ a population-based approach in which distributions of contact rates are approximated using discrete population groups such as age groups (Wallinga et al., 2006). However, the use of global information can be practical in the nosocomial setting because healthcare facilities are limited in size. In addition, the information about contacts between individuals may be more available than in the case of urban community infection. We have obtained this information by analyzing medical records.

To measure the mortality, we have assumed that the patients always die after being infected, whereas healthcare workers do not. However, the results are robust with respect to the definition of mortality. The difference between (i) the pattern of infection events for the entire population (Figs. 3a, b, 5a, and 8a, c, e) and (ii) that for the patients (Figs. 3c, d, 5b, and 8b, d, f) is unnoticeable, even quantitatively. This implies that, even if all the infected individuals are assumed to eventually die (corresponding to (i)), or healthcare workers die of infection with an intermediate probability (corresponding to mixture of (i) and (ii)), the results would rarely change. In addition, the results are expected to be robust against reduction in the case fatality of patients because reinterpretation of a fraction of state R patients as being recovered instead of dead little changes the results.

There are some limitations to the current work. First, we have neglected the weight of edges, or equivalently, heterogeneity in the transmission rate of individuals, except partial consideration in interventions 1 and 2 and in the sensitivity analysis. In reality, a Pt–Pt edge may be stronger than a Pt–Dr edge because the patients in the same room spend much time together, whereas a doctor examines a patient possibly for a couple of minutes per day. We have ignored this factor because the information available is limited (but see Bansal et al., 2006) and because the actual edge weights will depend on the type of diseases. Related to this, we have assumed frequency-dependent transmission in which the infection rate is proportional to the number of edges involved. Although this assumption is valid for sexually transmitted diseases (Lloyd-Smith et al., 2004), whether this assumption holds for nosocomial pathogens is not known.

Second, our networks do not include some types of relations and individuals. For example, there are three medical doctors for diabetes and one doctor for infection control in the hospital. These specialist doctors examine patients belonging to different departments upon request. However, our medical records miss such Pt–Dr relations. These doctors are expected to interact with more wards than ordinary doctors to play a leading role in epidemic spreading. We have also neglected radiographers and pharmacists that interact with patients in multiple departments, and visitors that would link the hospital to the outside community. We have also omitted social contacts outside of official hospital business. For example, two doctors may be friends such that they have lunch together on a daily basis, and doctors in different teams may share a office.

Third, we have assumed the simple transmission rule defined by the SIR model. Nosocomial pathogens such as MRSA and VRE cause asymptomatic infection in which carriers, of which there are many types, do not necessarily infect others. In the SIR model, incubation periods are ignored and all the individuals are as susceptible and infectious as others at a common infection rate. However, given the robustness of our results against heterogeneous infection rates for different individuals shown

in Section 3.3.4, we expect that our finding is extended to more general situations of disease spreading. Modeling dynamics of particular nosocomial pathogens is an important future problem.

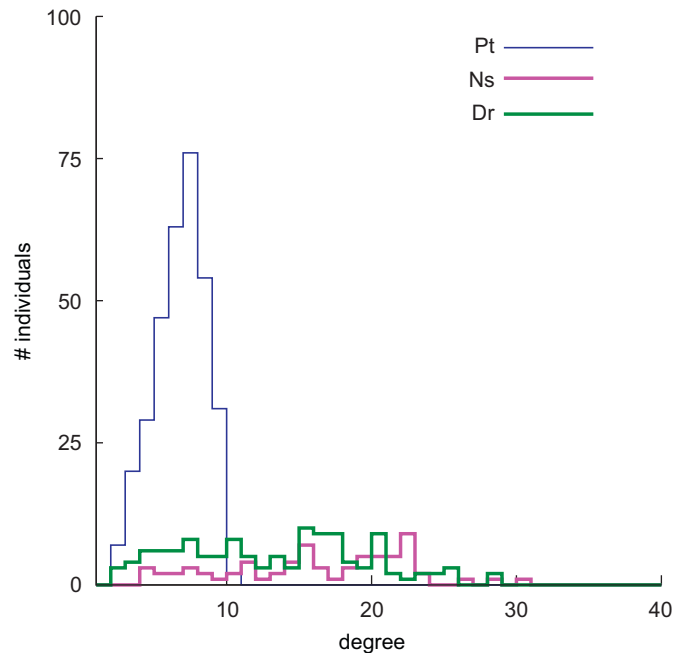Fourth, we have not considered dynamics of social networks (Volz and Meyers, 2007), except that we have confirmed that the main results are qualitatively the same at two time points (see Appendix for the other data set). In reality, the members of a hospital change on a very short time scale due to, for example, admission and discharge of patients (Bootsma et al., 2006; Liljeros et al., 2007).

In conclusion, the present study examined the spread of nosocomial infection in explicitly structured and observation-based social networks in a hospital, emphasizing the importance of controlling medical doctors as a potential major vector of diseases. Despite the necessity of various improvements, we believe that our exercise highlights specific hierarchical structure of social networks of hospitals and associated disease spreading patterns.

Appendix A. Results for the weekend network

In the main text, we explained the numerical results for the weekday network data. We show the results for the weekend network data in Figs. A1–A4, and Table A1. The main results are qualitatively the same at these two time points. Some differences are in the relative effectiveness of the class-based vaccination strategies (Fig. A4c–f).
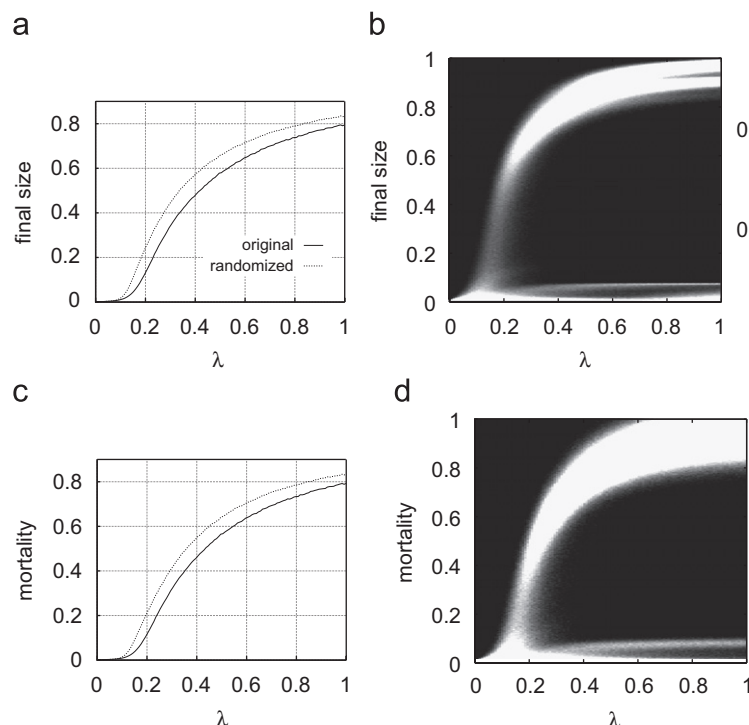

Fig. A1. Degree distributions of the weekend network for different classes of individuals.

Fig. A2. Disease spread in the weekend network. (a) Final size for the original network (solid lines) and the randomized network (dashed lines). (b) Distribution of the final size. (c) Fraction of mortality. (d) Distribution of the fraction of mortality. For a fixed λ, the upper masses of the distributions shown in (b) and (d) actually consist of two peaks nearby. This is because just a single junior doctor links the ward devoted to the psychiatry department with 39 (of 521) individuals to the rest of the network.
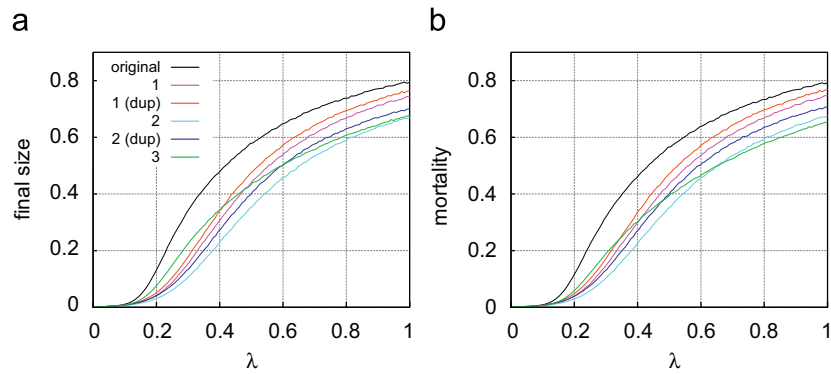
Fig. A3. Effects of different intervention protocols for the weekend network. (a) Final size and (b) fraction of mortality. Different lines correspond to the original observed network ('original'), networks after intervention 1 ('1'), intervention 1 with edge duplication ('1 (dup)'), intervention 2 ('2'), intervention 2 with edge duplication ('2 (dup)'), and intervention 3 ('3'). See Table A1 for the number of edges for the networks before and after interventions.
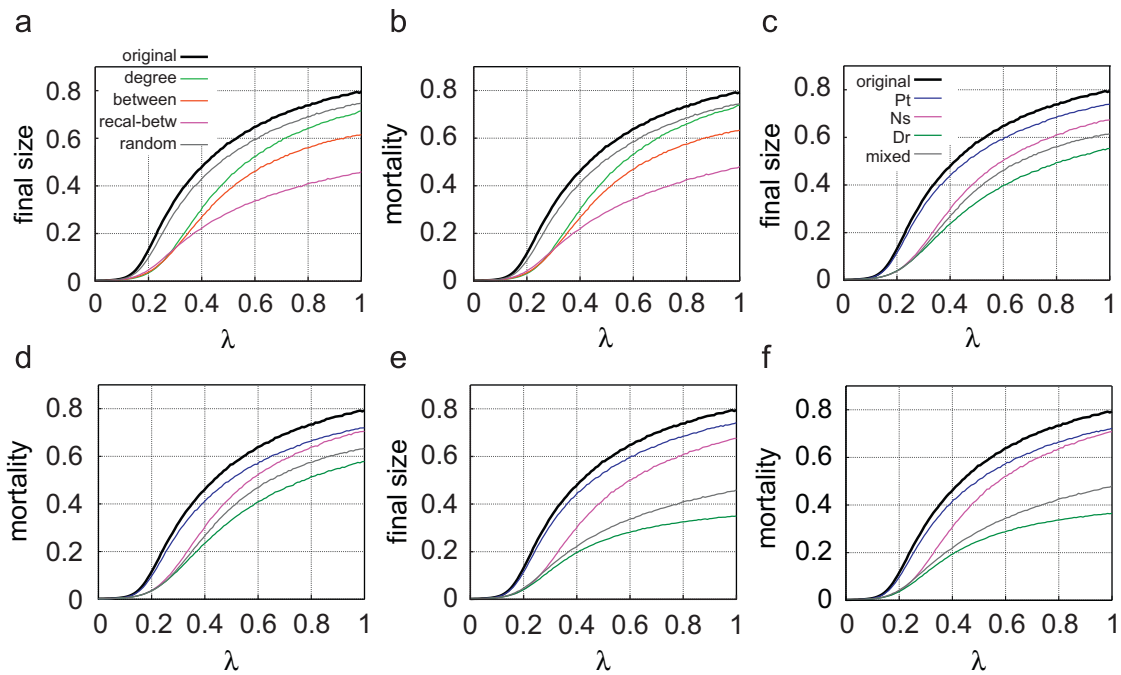

Fig. A4. Effects of vaccination strategies for the weekend network. (a) Final size and (b) mortality for different centrality-based and random vaccination strategies. Different lines correspond to the original observed network ('original'), degree-based vaccination ('degree'), betweenness-based vaccination ('between'), vaccination based on the recalculated betweenness centrality ('recal-betw'), and random vaccination ('random'). (c) Final size and (d) mortality for the vaccination strategy based on the betweenness centrality and the class of individuals. (e) Final size and (f) mortality for the vaccination strategy based on the recalculated betweenness centrality and the class of individuals. In (c)–(f), different lines correspond to the original network ('original'), Pt-first protocol ('Pt'), Ns-first protocol ('Ns'), Dr-first protocol ('Dr'), and class-mixed protocol ('mixed').

Table A1
The number of individuals and each type of edges for the original weekend network and the networks after intervention

Type of edge	Original	1	1 (dup)	2	2 (dup)	3
Total	2364	2168	2346	2094	2335	1872
Pt–Pt	492	492	492	492	492	0
Pt–Ns	329	329	329	329	329	329
Pt–Dr	753	710	753	675	753	753
Ns–Ns	124	124	124	124	124	124
Ns–Dr	513	378	513	350	513	513
Dr–Dr	153	135	135	124	124	153

Type of individuals						Number
Total						521
Pt						329
Ns						69
Dr						123

References

Albert, R., Jeong, H., Barabási, A.-L., 2000. Error and attack tolerance of complex networks. Nature 406, 378–382.

Anderson, R.M., Medley, G.F., May, R.M., Johnson, A.M., 1986. A preliminary study of the transmission dynamics of the human immunodeficiency virus (HIV), the causative agent of AIDS. IMA J. Math. Appl. Med. Biol. 3, 229–263.

Bansal, S., Pourbohloul, B., Meyers, L.A., 2006. A comparative analysis of influenza vaccination programs. PLoS Med 3, e387.

Boldin, B., Bonten, M.J., Diekmann, O., 2007. Relative effects of barrier precautions and topical antibiotics on nosocomial bacterial transmission: results of multi-compartment models. Bull. Math. Biol. 69, 2227–2248.

Bootsma, M.C., Diekmann, O., Bonten, M.J., 2006. Controlling methicillin-resistant Staphylococcus aureus: quantifying the effects of interventions and rapid diagnostic testing. Proc. Natl. Acad. Sci. USA 103, 5620–5625.

Burls, A., Jordan, R., Barton, P., Olowokure, B., Wake, B., Albon, E., Hawker, J., 2006. Vaccinating healthcare workers against influenza to protect the vulnerable—is it a good use of healthcare resources? A systematic review of the evidence and an economic evaluation. Vaccine 24, 4212–4221.

Carman, W.F., Elder, A.G., Wallace, L.A., McAulay, K., Walker, A., Murray, G.D., Scott, D.J., 2000. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomized controlled trial. Lancet 355, 93–97.

CDR weekly. 15, February 24, 2005. News stories: Influenza A outbreak in a community hospital in south east Wales where few healthcare workers had received immunization.

Cepeda, J.A., Whitehouse, T., Cooper, B., Hails, J., Jones, K., Kwaku, F., Taylor, L., Hayman, S., Cookson, B., Shaw, S., Kibbler, C., Singer, M., Bellingan, G., Wilson, A.P., 2005. Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: prospective two-centre study. Lancet 365, 295–304.

Christley, R.M., Pinchbeck, G.L., Bowers, R.G., Clancy, D., French, N.P., Bennett, R., Turner, J., 2005. Infection in social networks: using network analysis to identify high-risk individuals. Am. J. Epidemiol. 162, 1024–1031.

Cohen, R., Havlin, S., Ben-Avraham, D., 2003. Efficient immunization strategies for computer networks and populations. Phys. Rev. Lett. 91, 247901.

Colizza, V., Barrat, A., Barthélemy, M., Vespignani, A., 2006. The role of the airline transportation network in the prediction and predictability of global epidemics. Proc. Natl Acad. Sci. USA 103, 2015–2020.

Cooper, B., Lipsitch, M., 2004. The analysis of hospital infection data using hidden Markov models. Biostatistics 5, 223–237.

Cooper, B.S., Stone, S.P., Kibbler, C.C., Cookson, B.D., Roberts, J.A., Medley, G.F., Duckworth, G., Lai, R., Ebrahim, S., 2004. Isolation measures in the hospital management of methicillin resistant Staphylococcus aureus (MRSA): systematic review of the literature. Br. Med. J. 329, 533–540.

Elder, A.G., O'Donnell, B., McCruden, E.A., Symington, I.S, Carman, W.F., 1996. Incidence and recall of influenza in a cohort of Glasgow healthcare workers during the 1993-4 epidemic: results of serum testing and questionnaire. Br. Med. J. 313, 1241–1242.

Ferguson, N.M., Donnelly, C.A., Anderson, R.M., 2001. The Foot-and-Mouth epidemic in Great Britain: pattern of spread and impact of interventions. Science 292, 1155–1160.

Forrester, M, Pettitt, A.N., 2005. Use of stochastic epidemic modeling to quantify transmission rates of colonization with methicillin-resistant Staphylococcus aureus in an intensive care unit. Infect. Control Hosp. Epidemiol. 26, 598–606.

Forrester, M.L., Pettitt, A.N., Gibson, G.J., 2007. Bayesian inference of hospital-acquired infectious diseases and control measures given imperfect surveillance data. Biostatistics 8, 383–401.

Freeman, L.C., 1979. Centrality of Networks. Soc. Netw. 1, 215–239.

Gastmeier, P., Stamm-Balderjahn, S., Hansen, S., Nitzschke-Tiemann, F., Zuschneid, I., Groneberg, K., Rüden, H., 2005. How outbreaks can contribute to prevention of nosocomial infection: analysis of 1,022 outbreaks. Infect. Control Hosp. Epidemiol. 26, 357–361.

Girvan, M., Newman, M.E.J., 2002. Community structure in social and biological networks. Proc. Natl. Acad. Sci. USA 99, 7821–7826.

Green, D.M., Kiss, I.Z., Kao, R.R., 2006. Parameterization of individual-based models: comparisons with deterministic mean-field models. J. Theor. Biol. 239, 289–297.

Grundmann, H., Hellriegel, B, 2006. Mathematical modelling: a tool for hospital infection control. Lancet Infect. Dis. 6, 39–45.

Hethcote, H.W., Yorke, J.A., 1984. Gonorrhea: transmission and Control. In: Lecture Notes in Biomathematics, vol. 56, pp. 1–105.

Ho, A.S., Sung, J.J.Y., Chan-Yeung, M., 2003. An outbreak of severe acute respiratory syndrome among hospital workers in a community hospital in Hong Kong. Ann. Intern. Med. 139, 564–567.

Holme, P., Kim, B.J., Yoon, C.N., Han, S.K., 2002. Attack vulnerability of complex networks. Phys. Rev. E Stat. Nonlin. Soft Matter Phys. 65, 056109.

Ichinomiya, T., 2007. Analysis of the susceptible-infected-susceptible model on complex network. In: Proceedings of the International Symposium on Topological Aspects of Critical Systems and Networks, pp. 24–29.

Junker, B.H., Koschützki, D., Schreiber, F., 2006. Exploration of biological network centralities with CentiBiN. BMC Bioinformatics 7, 219.

Keeling, M.J., Eames, K.T.D., 2005. Networks and epidemic models. J. R. Soc. Interface 2, 295–307.

Leung, G.M., Hedley, A.J., Ho, L.M., Chau, P., Wong, I.O., Thach, T.Q., Ghani, A.C., Donnelly, C.A., Fraser, C., Riley, S., Ferguson, N.M., Anderson, R.M., Tsang, T., Leung, P.Y., Wong, V., Chan, J.C., Tsui, E., Lo, S.V., Lam, T.H., 2004. The epidemiology of severe acute respiratory syndrome in the 2003 Hong Kong epidemic: an analysis of all 1755 patients. Ann. Intern. Med. 141, 662–673.

Liljeros, F., Giesecke, J., Holme, P., 2007. The contact network of inpatients in a regional healthcare system: a longitudinal case study. Math. Popul. Stud. 14, 269–284.

Liljeros, F., Edling, C.R., Amaral, L.A., Stanley, H.E., Åberg, Y., 2001. The web of human sexual contacts. Nature 411, 907–908.

Lipsitch, M., Bergstrom, C.T., Levin, B.R., 2000. The epidemiology of antibiotic resistance in hospitals: paradoxes and prescriptions. Proc. Natl. Acad. Sci. USA 97, 1938–1943.

Lloyd-Smith, J.O., Getz, W.M., Westerhoff, H.V., 2004. Frequency-dependent incidence in models of sexually transmitted diseases: portrayal of pair-based transmission and effects of illness on contact behaviour. Proc. R. Soc. B 271, 625–634.

Meyers, L.A., Newman, M.E.J., Martin, M., Schrag, S., 2003. Applying network theory to epidemics: control measures for Mycoplasma pneumoniae outbreaks. Emerg. Infect. Dis. 9, 204–210.

Meyers, L.A., Pourbohloul, B., Newman, M.E.J., Skowronski, D.M., Brunham, R.C., 2005. Network theory and SARS: predicting outbreak diversity. J. Theor. Biol. 232, 71–81.

Palla, G., Derényi, I., Farkas, I., Vicsek, T., 2005. Uncovering the overlapping community structure of complex networks in nature and society. Nature 435, 814–818.

Pastor-Satorras, R., Vespignani, A., 2001. Epidemic spreading in scale-free networks. Phys. Rev. Lett. 86, 3200–3203.

Pelupessy, I., Bonten, M.J.M., Diekmann, O., 2002. How to assess the relative importance of different colonization routes of pathogens within hospital settings. Proc. Natl. Acad. Sci. USA 99, 5601–5605.

Perencevich, E.N., Fisman, D.N., Lipsitch, M., Harris, A.D., Morris Jr, J.G., Smith, D.L., 2004. Projected benefits of active surveillance for vancomycin-resistant enterococci in intensive care units. Clin. Infect. Dis. 38, 1108–1115.

Pourbohloul, B., Meyers, L.A., Skowronski, D.M., Krajden, M., Patrick, D.M., Brunham, R.C., 2005. Modeling control strategies of respiratory pathogens. Emerg. Infect. Dis. 11, 1249–1256.

Riley, S., 2007. Large-scale spatial-transmission models of infectious disease. Science 316, 1298–1301.

Salgado, C.D., Farr, B.M., Calfee, D.P., 2003. Community-acquired methicillin-resistant Staphylococcus aureus: a meta-analysis of prevalence and risk factors. Clin. Infect. Dis. 36, 131–139.

Svoboda, T., Henry, B., Shulman, L., Kennedy, E., Rea, E., Ng, W., Wallington, T., Yaffe, B., Gournis, E., Vicencio, E., Basrur, S., Glazier, R.H., 2004. Public health measures to control the spread of the severe acute respiratory syndrome during the outbreak in Toronto. N. Engl. J. Med. 350, 2352–2361.

Volz, E., Meyers, L.A., 2007. Susceptible-infected-recovered epidemics in dynamic contact networks. Proc. R. Soc. B 274, 2925–2933.

Wallinga, J., Teunis, P., Kretzschmar, M., 2006. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. Am. J. Epidemiol. 164, 936–944.

Watts, D.J., Strogatz, S.H., 1998. Collective dynamics of 'small-world' networks. Nature 393, 440–442.

Watts, D.J., Muhamad, R., Medina, D.C., Dodds, P.S., 2005. Multiscale, resurgent epidemics in a hierarchical metapopulation model. Proc. Natl. Acad. Sci. USA 102, 11157–11162.