

Using Sensor Networks to Study the Effect of Peripatetic Healthcare Workers on the Spread of Hospital-Associated Infections

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Background. Super-spreading events, in which an individual with measurably high connectivity is responsible for infecting a large number of people, have been observed. Our goal is to determine the impact of hand hygiene noncompliance among peripatetic (eg, highly mobile or highly connected) healthcare workers compared with less-connected workers.

Methods. We used a mote-based sensor network to record contacts among healthcare workers and patients in a 20-bed intensive care unit. The data collected from this network form the basis for an agent-based simulation to model the spread of nosocomial pathogens with various transmission probabilities. We identified the most- and least-connected healthcare workers. We then compared the effects of hand hygiene noncompliance as a function of connectedness.

Results. The data confirm the presence of peripatetic healthcare workers. Also, agent-based simulations using our real contact network data confirm that the average number of infected patients was significantly higher when the most connected healthcare worker did not practice hand hygiene and significantly lower when the least connected healthcare workers were noncompliant.

Conclusions. Heterogeneity in healthcare worker contact patterns dramatically affects disease diffusion. Our findings should inform future infection control interventions and encourage the application of social network analysis to study disease transmission in healthcare settings.

To understand how infections spread, one must understand how the agents under study move and interact. Many mathematical models used to explain the spread of infections assume random mixing. However, this assumption is known to produce misleading results even in studies outside of hospital settings [1]. Given the pattern of close and repeated contacts between healthcare workers (HCWs) and patients and

the presence of architectural constraints, it is unlikely that the random mixing assumption is warranted in healthcare settings. Indeed, observational studies suggest that different types of HCWs exhibit dramatically different contact patterns (in terms of both diversity and number) with other HCWs and patients [2]. Such high contact pattern variability suggests that some HCWs may have outsized influence on the spread of infections by virtue of sheer number and diversity of contacts. Models that assume the existence of peripatetic HCWs (ie, HCWs having an unusually large and diverse set of contacts) demonstrate that such highly connected HCWs may affect the dynamics of disease diffusion in healthcare settings. For example, Temime et al used simulations based on a hypothetical intensive care unit along with specific assumptions about HCW and patient interactions to demonstrate that hand hygiene noncompliance in a

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single peripatetic HCW can substantially affect the spread of healthcare-associated infections (HAIs) [3].

In this study, we used actual HCW movement data collected from a network of wearable sensors to confirm the existence of peripatetic HCWs in a hospital setting and to determine the impact of hand hygiene noncompliance in the presence of peripatetic HCWs.

METHODS

Data Acquisition

As part of a process improvement project to measure hand hygiene behavior, we deployed a set of wearable sensors to capture detailed location (eg, in a particular patient's room, at the nurses' station) and interaction data for 3 different categories of HCWs in the University of Iowa Hospitals and Clinics' Medical Intensive Care Unit (MICU) for both day and night shifts (a total of 6 distinct HCW types). This wireless sensor network consists of small credit card-sized wearable devices called motes: active, battery-powered, programmable devices containing a processor, flash memory, and an IEEE 802.15.4-compliant wireless radio. Each mote is programmed to broadcast a brief message at regular intervals (5 or 6 times a minute). When received by other motes within range, we obtain three pieces of data: (1) the identifier of the mote that sent the message; (2) the received signal strength (RSSI); and (3) the time the message was received. These data are recorded in the receiving mote's flash memory. The motes communicate over unused space in the Wi-Fi spectrum, do not interfere with medical devices, and, because they do not rely on fixed infrastructure, are easy to deploy [4].

We placed fixed-location motes, or beacons, in all 20 single-patient rooms in our MICU and also outside all patient rooms in commonly shared patient care areas (ie, hallways and nurses' stations), forming a framework of spatial reference points with which we can accurately estimate the location of other motes through triangulation.

In addition to beacons, we distributed wearable motes, or badges, to all HCWs assigned to work in the MICU. Technically, badges are identical to beacons in capability, but differ physically (wearable badges are packaged in recycled pager cases). By merging the data stored in each badge, we can reconstruct when the HCW wearing the badge entered a particular patient room, for example.

We deployed badges and collected data from all the MICU HCWs over a period of 7 days. Every morning at 7 AM we distributed badges to each HCW, and we collected the badges at 7 PM. New badges were distributed to night-shift workers at 7 PM and then collected the following morning at 7 AM. Once the badges were collected, their memory contents were offloaded to a server, and the badges were reset and recharged for use the next day.

Each badge was assigned a unique identification number associated with 1 of 3 HCW categories: nurses (ie, MICU floor nurses, nursing assistants, and nurse managers; day mean, 11.8; night mean, 8.1), doctors (ie, staff physicians, fellows, and residents; day mean, 7.1; night mean, 1.7), and critical support (ie, clerks, pharmacists, and respiratory therapists; day mean, 1.5; night mean, 1.8). Badges were assigned at random within categories: because of privacy concerns, we did not record the association between badge identification number and the HCW wearing the badge. Shifts were thus treated as independent collections of events. This badge distribution protocol was designed to prevent identification of individual workers; no HCW could be tracked across multiple shifts. Because no patient-specific identifiers or clinical data were collected for this process improvement project, it was ruled as nonhuman subjects research by our institutional review board.

Data from individual badges were merged by timestamp to produce a chronological log of all messages received by any badge over the course of each shift. From this log, we were able to reconstruct the physical contacts between individual HCWs and between HCWs and fixed-location beacons (a *contact* is defined as a time period where both motes recorded each other's presence above a predefined minimal RSSI for at least 30 seconds). Using the recorded RSSI and triangulation with known beacon locations, as well as knowledge about which patient rooms were occupied at any given time, we were able to detect hand hygiene opportunities occurring whenever a HCW entered or left a patient room as well as localize contacts between HCWs wearing badges in the unit outside the patient rooms.

Model

Based on the data collected, we performed a simulation, where HCW-HCW and HCW-patient contacts were replayed and used as the basis for an agent-level simulation, with parameters describing, probabilistically speaking, how infection spreads from agent to agent.

We based our infection and handwashing model closely on that used by Temime et al to simulate the spread of organisms by direct contact (eg, methicillin-resistant *Staphylococcus aureus*) [3]. We used 2 disease-based parameters: duration (D) and transmissibility (P). Duration was set at 10 days, which Temime et al suggest might reflect a weekly bacterial screening plus a 3-day wait for test results. We varied transmissibility from 0.0005 to 0.005 for each 30-second contact interval (corresponding to a 2%–18% chance of transmission during a single 20 minute contact, or roughly the same range used in Temime et al [3]). We assume HCW-HCW, HCW-patient, and patient-HCW transmissions are all equally probable.

We fixed handwashing effectiveness at $\lambda = 0.58$ (soap and water) or $\lambda = 0.83$ (alcohol rub) consistent with the rates reported in Girou et al [5]. We also assumed a baseline hand

Table 1. Model Parameters

Symbol	Definition	Range
P	Probability of transmission per 30 seconds of contact	0.0005–0.0050
D	Duration of pathogen colonization before treatment	10 days
λ	Hand hygiene efficacy	0.58 (soap), 0.83 (rub)
γ	Hand hygiene baseline compliance	$\mu = 0.25, 0.50, 0.75$ $\sigma = 0.10$
ε	Environmental contamination transmission rate	0.00–0.01

hygiene adherence rate, γ , in order to model typical low compliance ($\gamma = 0.25$), medium compliance ($\gamma = 0.50$), and high compliance ($\gamma = 0.75$) settings, respectively (the compliance rate of 50% is consistent with Temime et al [3] and other measurements of hand hygiene adherence in healthcare settings [6–8]). The parameters used in the model are shown in Table 1.

Agent-Based Simulations

We modeled the spread of nosocomial pathogens using an agent-based, discrete-event simulator of our own design that replays individual HCW–HCW and HCW–patient contacts and hand hygiene opportunities reconstructed from the data collected in the MICU. We defined a hand hygiene opportunity as a HCW entering or leaving a patient room. Each simulation uses contact data from 1 of 4 different representative MICU work shifts (2 day shifts, 7 AM–7 PM, and 2 night shifts, 7 PM–7 AM). The 2 day shifts track 27 or 19 HCWs and 19 or 18 patient beds, respectively, whereas the 2 night shifts track 19 or 14 HCWs and 18 or 19 patient beds, respectively. Fewer HCWs were tracked at night due to the lighter staffing levels typical of these shifts. During each shift, the notes recorded hundreds of thousands of messages. We discarded messages that did not meet predeployment calibration criteria indicative of close physical proximity (ie, low signal strength or asymmetric reception).

Each simulation is characterized by a particular set of parameter values and replays one shift’s contact pattern 30 times sequentially for a total of 360 synthetic MICU contact hours (because privacy concerns preclude conserving identities across shifts, replicating and concatenating a single shift is the most natural means to extend the simulation over multiple days). Moreover, because the simulations are nondeterministic, each 360-hour simulation is replicated 1000 times (using randomly chosen initial conditions), and aggregate results (eg, means, medians) are reported.

Each replicate establishes a single, randomly selected infected patient and assigns each HCW a randomly selected compliance rate, γ_i , from a normal distribution with mean $\mu = \gamma$ and

fixed standard deviation of $\sigma = 0.10$. Noncompliant HCWs are assigned $\gamma_i = 0$. The simulator then replays the selected shift’s events 30 times. If the event is a contact between 1 infected and 1 uninfected individual, the infection is passed on with a probability P. An infected individual remains infected for D simulation periods unless an intervening hand hygiene opportunity results in an effective hand hygiene event, resetting the HCW’s infection status to uninfected with probability $\gamma_i \times \lambda$. An environmental parameter, ε , similarly regulates whether an uninfected HCW is infected by the environment between patient interactions.

For each 12-hour work shift, we determined both the peripatetic, or most connected, (deidentified) HCWs and the least connected (deidentified) HCWs (for comparison) based on the number of unique patients visited during that shift. Each simulation compares results for 7 distinct scenarios demonstrating the impact of peripatetic HCWs on infection rates:

- S1: All HCWs are equally compliant.
- S2: The single least-connected HCW is noncompliant.
- S3: The 2 least-connected HCWs are noncompliant.
- S4: One randomly selected HCW is noncompliant.
- S5: Two randomly selected HCWs are noncompliant.
- S6: The single most-connected HCW is noncompliant.
- S7: The 2 most-connected HCWs are noncompliant.

RESULTS

Existence of Peripatetic Healthcare Workers

Analysis of 48 hours (4 12-hour shifts) of University of Iowa Hospitals and Clinics’ MICU HCW contact data displayed heterogeneity in the number of contacts, number of distinct contacts, duration of contacts, and contacts between different categories of HCWs (eg, nurse–doctor contacts, nurse–nurse contacts).

In a typical daytime shift, the average number of contacts per HCW over a 12-hour period was 80.1 (median, 64; $k = 0.48$), and for a typical nighttime shift, the average was 76.1 (median, 22; $k = -1.34$). But these contact distributions vary significantly by individual shift (eg, day vs night) and contact type (eg, HCW–HCW vs HCW–patient). Yet, for nearly all of the shifts studied, the contact distributions were distinctly heavy tailed— that is, a small number of HCWs were responsible for a disproportionate share of the contacts (ie, similar to power law distributions). This property is clearly visible in the cumulative distribution functions for contact distributions (see Figure 1A and 1B). A similar property is noted in the cumulative distribution functions for the duration of these contacts (see Figure 1C and 1D). Healthcare workers whose individual contacts fall into the tail are peripatetic HCWs, given that increased diversity of contacts can only occur if the HCW is traveling from place to place at a greater rate.

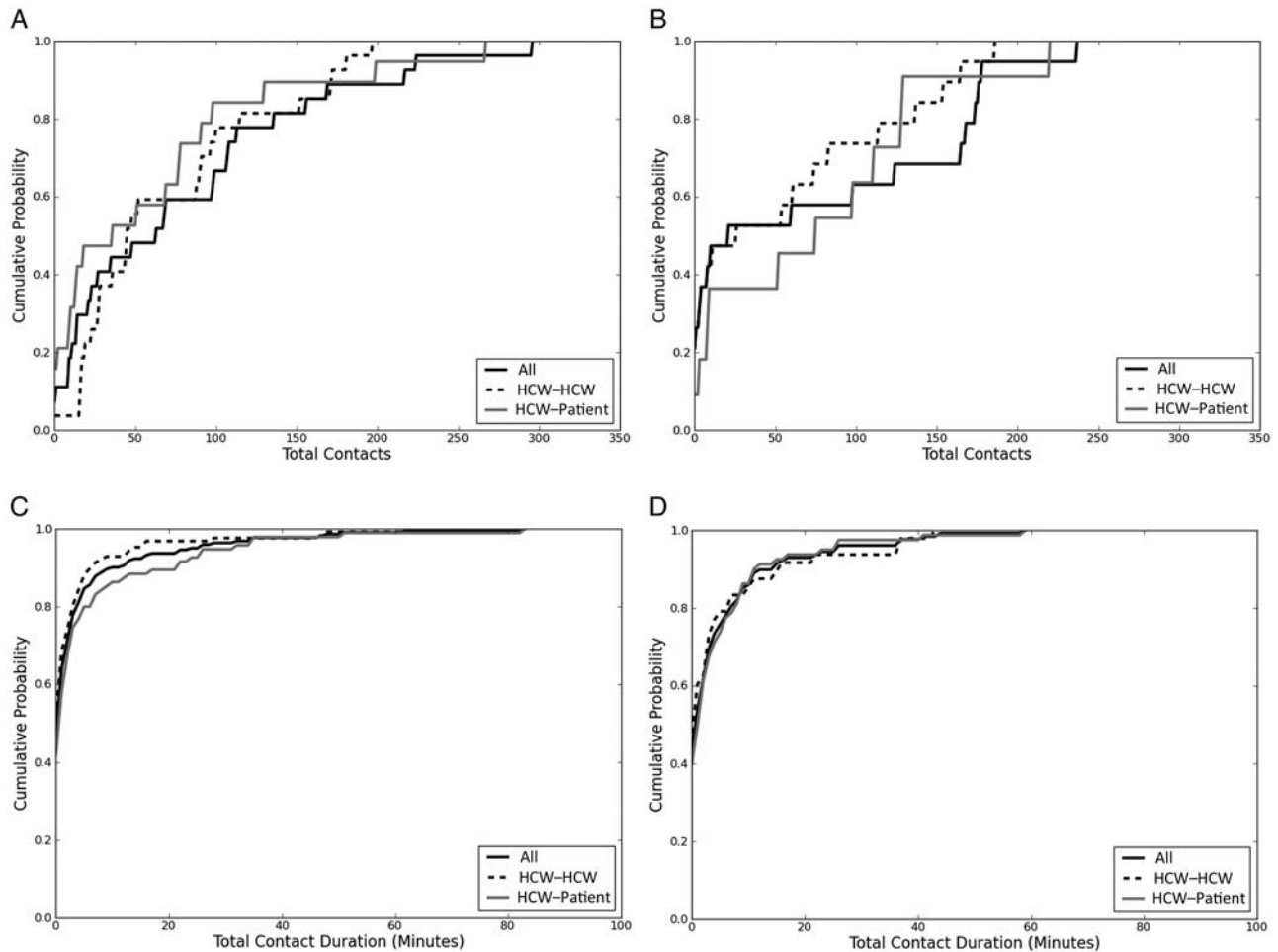


Figure 1. Healthcare worker [HCW] contact cumulative distribution functions for typical day shift (*A* and *C*) and night shift (*B* and *D*). Plots *A* and *B* describe the distribution of contacts observed over the course of a single shift. The distributions are fat tailed, with median values at about 50 contacts per shift (day, *A*) and <50 contacts per shift (night, *B*) but with maximum contacts at much higher values for both shifts (third-quartile values of 111.50 for day shift and 167.50 for night shift). The larger horizontal separation of the healthcare worker–HCW curve and HCW–patient curve in (*A* and *B*) reflects the difference between day shifts, where HCW–patient interactions are relatively more balanced, and night shifts, where the smaller number of HCWs on duty are more likely to interact with each other than with most patients. Plots *C* and *D* describe the distribution of contact durations; these are also fat tailed, with the median values in the 1-minute range. Notice that, although fewer in number, nighttime HCW–patient contacts (*D*) tend to be longer in duration.

Most contacts are of relatively short duration for both day and night shifts, with only a few contacts being of very long duration. In addition, most observed patterns were also uniform across HCW types: for example, doctor–patient and nurse–patient contacts were also heavy tailed, confirming that peripatetic HCWs are not necessarily constrained to a single type of HCW but exist in every HCW category.

Impact of Peripatetic Healthcare Workers on Infection Rates

Figure 2 shows the results obtained from simulations with a medium baseline compliance ($\gamma = 0.50$), alcohol-based rub ($\lambda = 0.83$), and no environmental contamination ($\epsilon = 0$). Each pair of plots shows mean and median values obtained

for each scenario over 1000 replicates as a function of transmissibility, P , for selected daytime and nighttime contact patterns. The plots confirm that the scenarios assort as expected in terms of infection outcomes; in other words, noncompliant peripatetic HCWs serve as outsized amplifiers of infection. These observations are consistent over the whole range of simulations: when soap and water ($\lambda = 0.58$) are used in lieu of alcohol-based rub (see Figure 3) or when environmental contamination ($\epsilon = 0.05$) is in play (see Figure 4). They also are consistently true across both day and night shifts: although the magnitude of the effect may differ, there is no discernible difference in the nature of the effect.

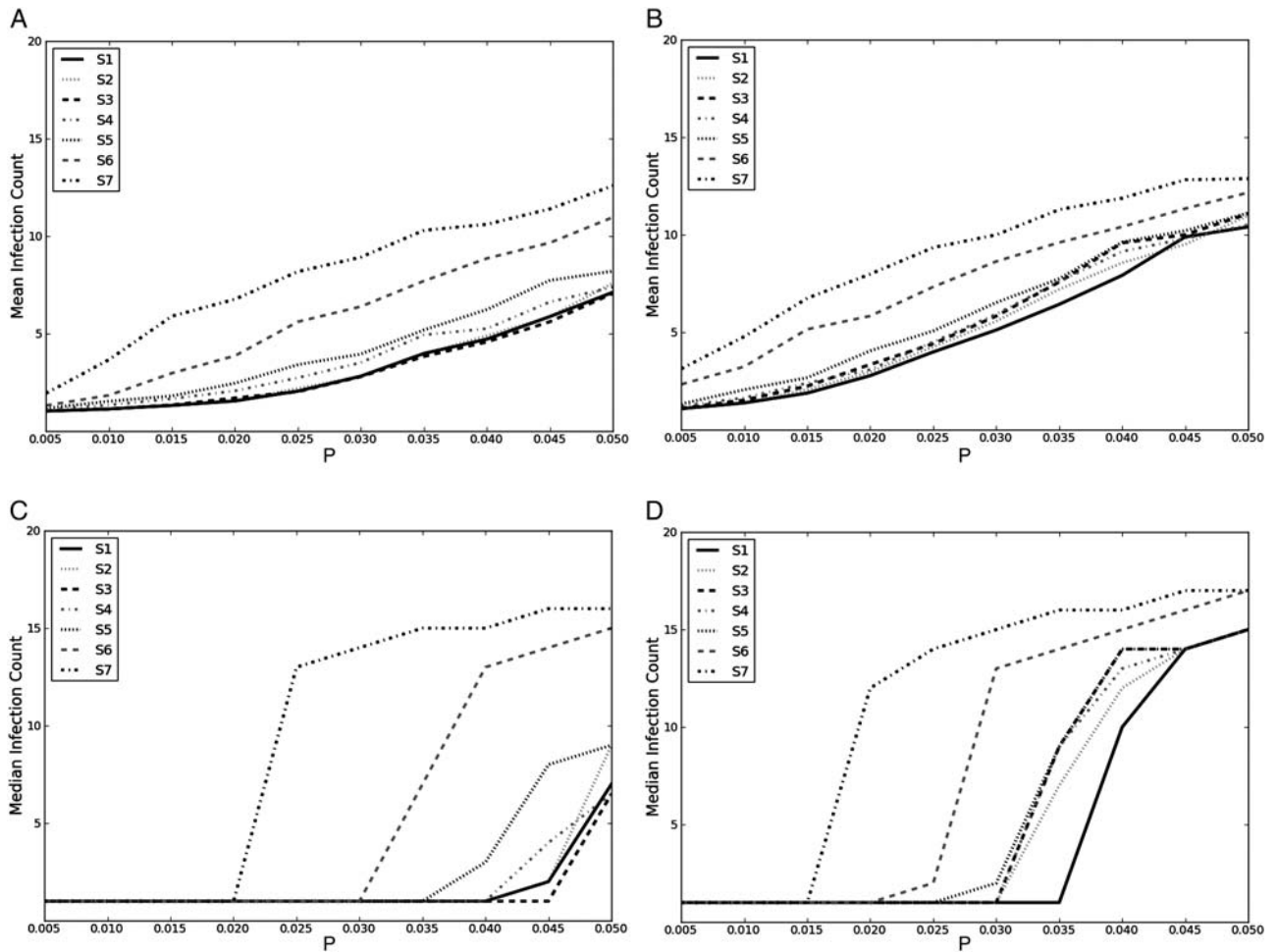


Figure 2. Aggregate infection counts for day-shift (A and C) and night-shift (B and D) simulations as a function of transmissibility. Each plot shows the aggregate outcomes (means in A and B; corresponding medians in C and D) obtained over 1000 replicates of 360 hours of synthetic medical intensive care unit contact hours for all 7 standard scenarios: S1 (all healthcare workers [HCWs] are equally compliant), S2 (the single least-connected HCW is noncompliant), S3 (the 2 least-connected HCWs are noncompliant), S4 (1 randomly selected HCW is noncompliant), S5 (2 randomly selected HCWs are noncompliant), S6 (the single most-connected HCW is noncompliant), and S7 (the 2 most-connected HCWs are noncompliant). The simulations shown here correspond to a medium level baseline compliance ($\gamma=0.50$) with alcohol-based rub ($\lambda=0.83$) and no environmental contamination ($\epsilon=0$). The lowest possible infection counts are obtained with full compliance—that is, every HCW, i , has hand hygiene compliance, γ_i , drawn from a standard normal distribution ($\mu=\gamma$; standard deviation=0.1). When either 1 or 2 noncompliant HCWs are present, the best results are obtained when the least peripatetic HCW(s) is/are noncompliant ($\gamma_i=0$), and the worst results are obtained when the most peripatetic HCW(s) is/are noncompliant ($\gamma_i=0$); randomly selected noncompliant HCWs generally produce infection count results in between, although usually closer to the former. Comparing means (A and B) with medians (C and D) confirms that outcome distributions are very skewed; very high infection counts in a few replicates tend to pull mean values up, even if most replicates produce very low infection counts. Plotting medians makes clear, for example, that with low transmission rates, the initial infection does not spread beyond the initially infected patient.

Results are reported as both average and median number of patients infected over 1000 replicates because the distribution of outcomes within replicates is quite skewed. More specifically, when transmissibility is low, transmission does not occur in many of the replicates, meaning that disease often does not spread beyond the originally infected patient. In such cases, the median values are more indicative of the expected behavior because the mean values can be unduly influenced by just a few replicates where the infection affects a large number of agents.

Comparing Figures 2 and 3 demonstrates the impact of improving the effectiveness of hand hygiene. Less-effective hand hygiene, represented here by the use of soap and water ($\lambda=0.58$; see Figure 3) rather than an alcohol-based solution ($\lambda=0.83$; see Figure 2), does increase the expected infection count, as can be seen by the slight upward shift in the upper panels of Figure 3 with respect to the upper panels of Figure 2. A similar effect is noticeable in the lower panels, where some of the median curves in Figure 3 are shifted

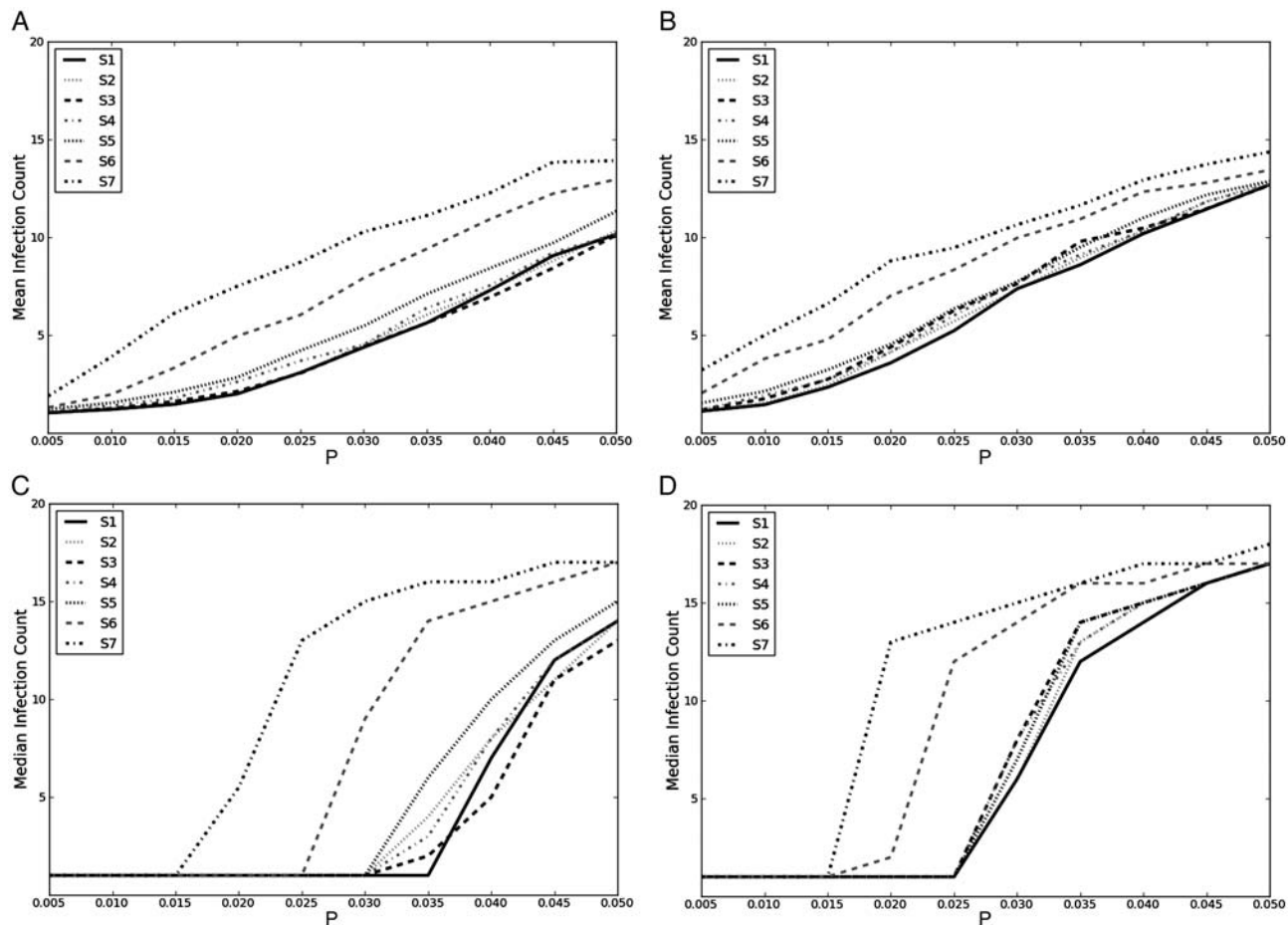


Figure 3. Aggregate infection counts for day-shift (A and C) and night-shift (B and D) simulations as a function of transmissibility for all 7 standard scenarios: S1 (all healthcare workers [HCWs] are equally compliant), S2 (the single least-connected HCW is noncompliant), S3 (the 2 least-connected HCWs are noncompliant), S4 (1 randomly selected HCW is noncompliant), S5 (2 randomly selected HCWs are noncompliant), S6 (the single most-connected HCW is noncompliant), and S7 (the 2 most-connected HCWs are noncompliant). The simulations shown here correspond to a medium level baseline compliance ($\gamma = 0.50$) with soap and water washing ($\lambda = 0.58$) and no environmental contamination ($\epsilon = 0$). The results are consistent with those observed in Figure 2 for alcohol-based rub, with all 7 standard scenarios assorting as expected.

slightly to the left and up with respect to the analogous curves in Figure 2.

Comparing Figures 2 and 4 demonstrates the impact of environmental contamination. When an HCW leaves a patient's room and $\epsilon > 0$, the HCW is colonized with the pathogen with probability ϵ . Increasing levels of environmental contamination attenuate the positive impact of hand hygiene on infection counts, in effect shifting the curves in the upper plots upward in Figure 4 with respect to Figure 2. Note, however, that the effect of environmental contamination is independent of the impact of noncompliant peripatetic HCWs; the curves for scenarios S6 and S7 are always well above the other curves in the upper plots of both Figures 2 and 4, although the lower plots of Figure 4 do indicate, by virtue of their greater median values with respect to Figure 2, that environmental contamination increases the likelihood that an infection will spread

beyond the initial patient. These trends continue as the value of ϵ increases, and similar effects are noted when comparing analogous plots based on soap and water protocols ($\lambda = 0.58$).

The results reported here and the general observations that accompany them are confirmed by similar plots for low and high baseline compliance ($\gamma = 0.25$ and $\gamma = 0.75$). In every case, who is not compliant with hand-hygiene practice is at least as important as the average compliance rate. For example, in every plot shown here, the infection count for scenario S6 greatly exceeds the infection count for scenario S5.

DISCUSSION

Our results generated by a real contact network clearly demonstrate the heterogeneous nature of HCW-HCW and HCW-patient contact patterns and also show the importance of

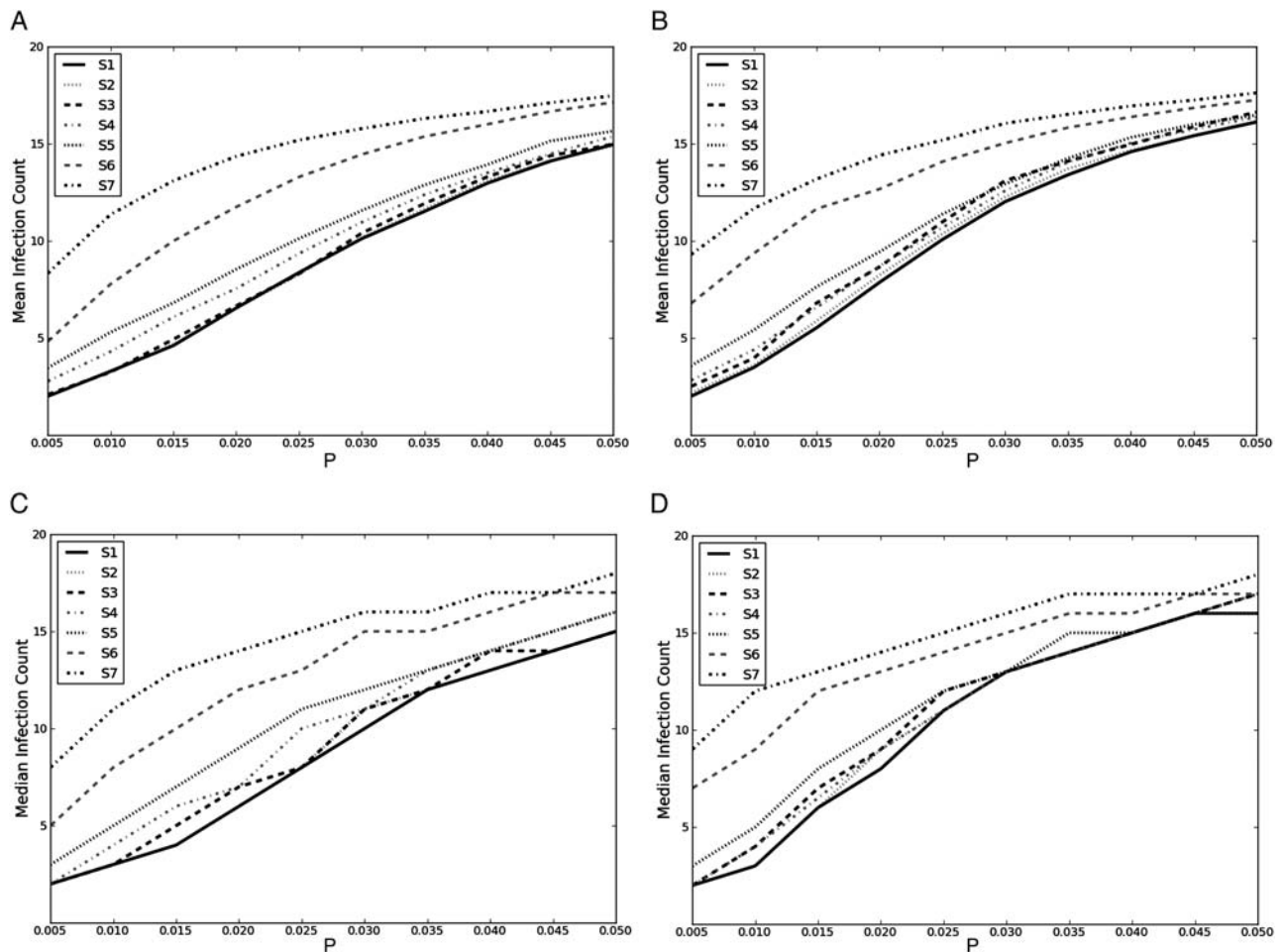


Figure 4. Aggregate infection counts for day-shift (*A* and *C*) and night-shift (*B* and *D*) simulations as a function of transmissibility for all 7 standard scenarios: S1 (all healthcare workers [HCWs] are equally compliant), S2 (the single least-connected HCW is noncompliant), S3 (the 2 least-connected HCWs are noncompliant), S4 (one randomly selected HCW is noncompliant), S5 (2 randomly selected HCWs are noncompliant), S6 (the single most-connected HCW is noncompliant), and S7 (the 2 most-connected HCWs are noncompliant). The simulations shown here correspond to a medium level baseline compliance ($\gamma = 0.50$) with alcohol-based rub ($\lambda = 0.83$) and some level of environmental contamination ($\epsilon = 0.05$). As before, all 7 standard scenarios assorting as expected, but here the mean (*A* and *B*) and median (*C* and *D*) plots are much less differentiated, reflecting the effect of environmental contamination on infection rates even when hand hygiene compliance is relatively good. Even with low transmission rates, median values are much higher (compare with Figure 2) for all 7 scenarios, reflecting the fact that the initial infection spreads beyond the initially infected patient in a larger proportion of replicates.

considering this heterogeneity in order to understand the spread of infections. Our findings have implications not only for designing models to measure the potential impact of infection control measures but also for auditing HCW behavior associated with such measures.

Healthcare-associated infections are a notable cause of morbidity and mortality and add greatly to the cost of healthcare delivery [9, 10]. However, opportunities to learn about HAIs are often limited to observing outbreaks. Furthermore, when outbreaks occur, multiple interventions are applied contemporaneously, making it difficult to tease apart the impact of individual interventions. For this reason, simulations based on mathematical models represent an important tool for

improving our understanding of HAIs, and they represent a useful approach to study the potential impact of interventions because one can isolate the effects of a particular intervention. Of course, the quality of a computational simulation is bounded by the explicit and implicit assumptions of the model as well as the accuracy and completeness of the underlying data driving the simulation. For logistical and technical reasons, the latter has historically been especially difficult, resulting in either sampling or simplifying assumptions about movement and interactions that may not accurately reflect real-world practice. Fortunately, new technology, embodied by our motes and similar wearable devices [11], can now be used to accurately measure contact patterns in healthcare settings.

One standard assumption used in many infectious disease models is to assume that populations mix randomly, essentially assuming all individuals move and interact uniformly (ie, the likelihood that any individual encounters any other individual is uniform). This assumption ignores 4 important features of human interactions in healthcare settings [1, 11]: (1) the large variability of potential contacts between patients and/or HCWs; (2) that any 2 individuals are connected by a surprisingly small number of transmission steps; (3) the architectural (spatial) constraints; and (4) the nonuniform clustering of human social contacts. Because our simulations are driven by extraordinarily complete and accurate contact tracking, we show that ignoring the inherent complexity of contact patterns in real-world healthcare settings can lead to misleading simulation results.

In addition, our results also highlight how simulations can be used to study the effectiveness of interventions to reduce the spread of HAIs and how important it is to consider heterogeneity because many of these interventions depend upon individual HCW behavior (eg, hand hygiene adherence, vaccination choice, wearing gowns and gloves for patients in contact isolation). Individual behavior is especially important because a significant proportion of HCWs do not adhere to infection control policies: indeed, hand hygiene rates <50% are often reported [6–8]. These rates are routinely tracked by infection control programs in an aggregate fashion [6, 12]. Our results suggest that aggregate rates may not reflect important variations at the individual level. For example, a unit with HCW hand hygiene rates approaching 90% may still have difficulties controlling the spread of infections if the noncompliant HCWs happen to be unusually connected. Moreover, although several studies demonstrate that improving hand hygiene can decrease HAIs [13, 14], increasing hand hygiene rates will not necessarily decrease infections [15]. Clearly HCWs' hands can harbor and transmit infectious agents to patients [14, 16, 17]. However, our results, which are consistent across a broad range of MICU work shifts (data not shown) and hand hygiene compliance rates, suggest that the measured effect of an intervention to improve hand hygiene compliance may depend on the nature of the HCWs eventually engaged by the intervention.

The existence of peripatetic HCWs should also change the way we collect information about hand hygiene and other HCW behavior. For example, the use of hand hygiene product has been proposed as a surrogate marker for hand hygiene compliance [18], yet product usage is an aggregate measure that is blind to the existence of peripatetic HCWs [3]. Note that direct observation, if not carefully implemented, can also fail to capture peripatetic effects.

Our study has several limitations. First, our simulations define hand hygiene opportunities as “in room” or “out of room”; these are easy for us to measure but fail to entirely

capture the World Health Organization 5 moments of hand hygiene [19]. Second, there was a brief 20–40-minute period between shifts during badge distribution where we did not capture contacts or hand hygiene opportunities. However, because the missing period corresponds to nursing report, when there are relatively fewer patient contacts, the coherence of our results was not unduly affected. Third, we did not distribute motes to HCWs who visited the unit to see patients in the MICU (eg, consulting physicians); however, our technology captured the overwhelming majority of HCW interactions, especially because consulting physicians interact for very limited periods of time with limited patients on the MICU. Fourth, our study was done in a single unit in a single medical center, and the results may not necessarily be generalizable to other settings. Finally, the disease diffusion parameters used in our study were largely obtained from the (very sparse) literature on objective measures of infectivity and transmissibility. Yet despite these limitations, our results demonstrate, using real data, the importance of considering HCW heterogeneity in understanding how infections spread within an intensive care unit.

Future modeling efforts should incorporate the kind of data generated by our sensor motes. Because traditional approaches to contact tracing are extremely labor intensive and often prone to measurement errors (eg, recall bias [20]), our sensor motes could also be used to estimate more accurate disease parameters. Because this wireless approach does not require any preexisting infrastructure and is therefore easy to deploy (usually within minutes), it could ultimately be used to estimate exposure to infectious patients and could thus be used to augment traditional contact tracings during outbreak investigations soon after an outbreak starts. For example, during an outbreak, our motes (now small enough to be incorporated into name badges) can be used to determine if HCWs came within 3–6 feet of other HCWs wearing motes and how long they spent in particular patient rooms. Indeed, the importance of measuring contacts and estimating exposure risk was highlighted during the severe acute respiratory syndrome outbreak, when it was not immediately clear if the disease was spread by a droplet or airborne route [21, 22]. Thus, in addition to informing mathematical models and infection control interventions, our mote-based approach could help assist with outbreak investigations.

Notes

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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