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Major Article

Network analysis of cases with methicillin-resistant *Staphylococcus aureus* and controls in a large tertiary care facility

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Background: Despite increased awareness of infection control precautions, methicillin-resistant *Staphylococcus aureus* (MRSA) still spreads through patients and contaminated objects, causing a substantial burden of illness and cost. Our objective was to define risk factors for contracting MRSA in a tertiary health care facility using a historic case-control study and to validate health care network changes during pre-outbreak and outbreak periods.
Methods: We conducted a case-control study using secondary data on hospitalizations where infected or colonized cases were compared with matched controls who tested negative by age, sex, and campus over 1 year. Social networks of all cases and controls were built from links joining patients to rooms, roommates, and health care providers over time.
Results: Matched controls were similar to cases in comorbidity, lengths of stay, mortality, and number of roommates, rooms, and health care providers. As expected, the number of rooms and roommates increased in the outbreak by more than 50%. A timed animation of the network at one campus identified potential source patients linked to 2 rooms and many roommates, after which cases connected to those same rooms proliferated.
Conclusions: Only the network animation over time revealed possible transmission of MRSA through the network, rather than attributes measured in the traditional case control study.

BACKGROUND

In Canada, in 2010, 4.2% of hospitalized patients became infected or colonized with methicillin-resistant *Staphylococcus aureas* (MRSA), resulting in a cost of US$28.3 million.[1,2] In 2012, approximately 9% of patients with MRSA outside of the bloodstream and 25% with bloodstream infections died 30 days after a positive culture.[3] Despite consistent prevention efforts, MRSA infections rose steadily from 0.51/1,000 patient-admissions in 1995 to 2.9/1,000 cases in 2009, after which they leveled off at 2.2/1,000 patient-admissions.[4,5] Whether MRSA cases are sporadic or part of a hospital outbreak, they are associated with increased length of hospital stay, morbidity, mortality, health care costs, and development of further antimicrobial resistance.[6]

Reservoirs of MRSA include colonized and infected patients, physicians, nurses, and technicians, who may remain undetected and continually expose others, as well as inanimate objects such as plastic charts. MRSA can survive for more than 60 days on many surfaces in the hospital, including glass, vinyl flooring, tile, and countertops.[7] Hand carriage of MRSA, other contact, and transmission among people, objects, and places are better represented as network interactions rather than by stand-alone places, objects, and/or people as in case-control studies.

Social network analysis (SNA) is the quantitative method used to visualize, describe, and investigate a set of items, events, or people

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Ethics approval and consent to participate: The Ottawa Hospital Science Network Research Ethics Board approved this study (OHSN-REB #20140794-01H) and waived the need for patient informed consent. In this observational study, we performed a retrospective extraction of administrative and clinical data from The Ottawa Hospital Data Warehouse. These data were de-identified and then used for network building and data analysis; therefore, this study involved secondary use of de-identified personal health information.
Availability of data and materials: We confirm that we do not wish to share The Ottawa Hospital datasets used in this study, as the datasets have high-risk fields (eg, contain patient health information). As a result, these datasets cannot be uploaded to an external, unsecure site or location.

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linked by relationships of some kind in a social network.[8-10] SNA has been used to better characterize person-to-person transmission of HIV,[11] sexually transmitted diseases,[12,13] tuberculosis,[14,15] and blood-borne pathogens among injection drug users,[16] as well the spread of other infectious diseases.[17-25] In one case-control study, SNA was the only method that defined a specific place of risk interaction as the cause of an outbreak.[26] Analyses of transmission networks have included both people and geographic or environmental exposures in specific places.[12,13,16,26-30] Only one study using SNA and electronic health records has shown that interactions among patients and health care workers (HCWs) influenced the transmission of MRSA in a neonatal intensive care unit (ICU) of a large tertiary care facility.[31]

OBJECTIVES

We wanted to further the knowledge of MRSA sources and transmission by testing the feasibility and validity of building hospital networks linking patients, rooms, and roommates against a case-control study to better identify the role of HCWs and places in the transmission of MRSA in a large tertiary care facility, using electronic medical record data.

METHODS

The Ottawa Hospital (TOH) is a 1,118-bed, academic tertiary care hospital in Ottawa, Ontario, Canada, spread over 3 campuses and an inpatient rehabilitation center that provides services for a population of 1.3 million in eastern Ontario and western Quebec. There are over 50,000 patient admissions annually.

Study Population

Adult inpatients, 18 years or older, admitted to any acute care campus of TOH between April 1, 2013, and March 31, 2014, were eligible for inclusion. During the study period, TOH Infection Prevention and Control Program confirmed 746 positive MRSA cases (colonizations and infections) at TOH. After an attempt to link data for the MRSA-positive cases (using patient medical record number and admission date) obtained from TOH Infection Prevention and Control Program to a valid inpatient encounter in TOH Database Warehouse (TOHDW),[32] and 2 case-control matching rounds (1:1 ratio, matched by age, campus, and gender), we were able to include 1,094 patients in the study (547 patients in each group).

Cases included patients who tested MRSA positive after diagnostic testing or screening. Targeted screening of patients at high risk for nasal and/or rectal MRSA colonization was conducted routinely on admission, as per hospital policy. High-risk patients included all those admitted to the intensive care unit, the rehabilitation center, or through the emergency department, or patients transferred internally to any inpatient TOH campus from another TOH campus or from another health care facility including long-term care facilities.[33] Screening was also conducted routinely on inpatient contacts of patients newly identified with hospital-acquired MRSA.

As per TOH Infection Prevention and Control Program MRSA case definitions, patients whose screening or clinical specimens yielded MRSA 48 hours or more after admission or in whom MRSA acquisition could be attributed to a previous hospitalization within the prior 2 months were considered to have hospital-acquired MRSA. In addition, those identified within 48 hours of admission and in whom there were no previous admissions within the past 2 months were considered to have community-acquired MRSA.

Controls were drawn randomly from eligible inpatients who were screened for MRSA at any time during their hospitalization and who remained MRSA negative for the duration of the study period. The controls that became cases later on during the study period were excluded, and another round of case matching was conducted. Controls were matched 1:1 with cases by age, gender, and campus and were selected prior to network construction, so their links were unknown.

Data analysis

Cases were linked by their medical record number and admission date to a valid inpatient encounter in TOHDW which was then used to select and match the controls with cases. TOHDW is a relational database that contains patient information from the patient registration system, clinical data (including laboratory, radiology, pharmacy, and clinical information), patient abstracts, and room occupancy. Complete records of attending physicians for each patient were available in TOHDW, though not for the other health care workers.

Cases and controls were paired with their roommates, rooms, and attending physicians in chronological order. Pajek 4.09,[34] a software program for analysis and visualization of very large networks, was used to build the networks (Fig 1). The rooms were subsections of a unit comprised of 1 to 3 beds with or without a bathroom, 4 beds with a bathroom, or an entire unit with beds separated by curtains and/or walls and at least 1 bathroom.

We evaluated the "connectedness" of groups of patients and places by counting groups of people and places with at least 1 link between them (components), as well as by the proportion of links existing in a component out of all those that could exist (density). Finally, we examined the immediate influence or importance of each person and place by the number of direct connections each one had (degree)[35,36]

Data collected for the entire study period resulted in very large, dense networks, which presented challenges in defining network boundaries, analysis, and visualization. Moreover, we wanted to validate the networks with epidemiological data. We defined the start of an MRSA outbreak as the first week in which the number of cases observed exceeded the moving 3-week average and twice the cumulative standard deviation of all previous weeks (expected),[37,38] which differed from the institution's definition. The first day of the week in which the outbreak was detected was designated the index day, and the previous 8 weeks as period 0 (pre-outbreak); the subsequent 8 weeks were designated as period 1 (outbreak period). Networks were built for cases and controls during the 2 reference periods.

The network was constructed from a paired list of all vertices representing patients connected to the rooms in which they stayed, their roommates who were in those rooms, and their attending physicians. For example, an MRSA patient seen by an attending physician who stayed in a room with 2 roommates would appear as a vertex (Fig 1, a red triangle) linked to another 4 vertices represented by a room (Fig 1, a blue square), 2 roommates (Fig 1, 2 green circles), and an attending physician (Fig 1, a purple diamond) for a total of 4 links. Pajek was used to draw the networks and calculate the density, number of vertices, links, and components (Table 2). The degree centrality of a vertex was calculated using UCINET for Windows.[39] We stratified the degree centrality by MRSA cases, places (patient rooms), and attending physicians. Wilcoxon-Mann-Whitney tests comparing the median degree centrality between cases and controls for the 2 reference periods were performed using SAS 9.4 (SAS Institute; Cary, NC).

We removed the emergency room from the networks because 72% of MRSA cases and 80% of controls had connections to it, and the number of links obscured the structure of the graph.

RESULTS

During the study period, 49,341 patients were admitted to TOH, of whom 746 were identified as having hospital- or community-acquired MRSA, and 547 of those met the definition of an MRSA

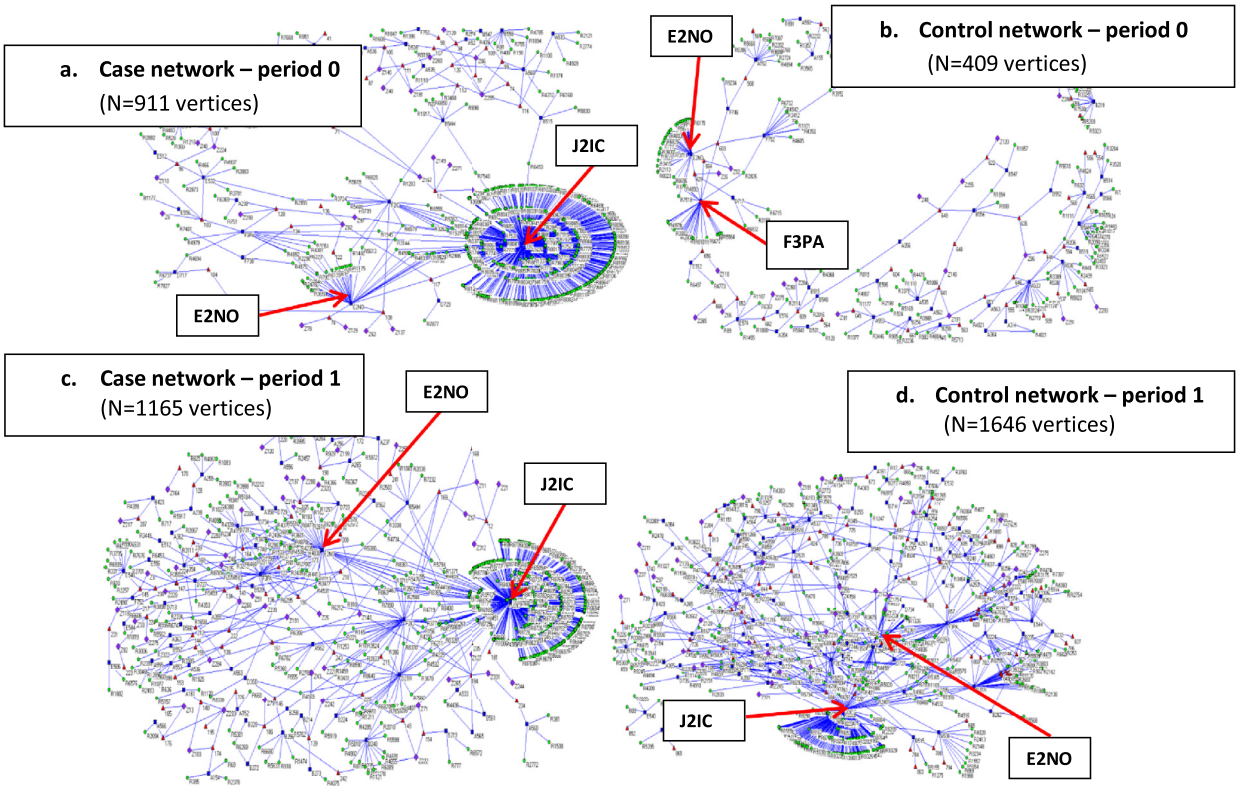

Fig 1. Comparison of period 0 (pre-outbreak) to period 1 (outbreak) cases networks and controls networks at Campus A. ▲, case or control; ■, room; ●, roommate; and ◆, attending physician. There were visible differences between both groups' networks during the 2 reference periods. During period 1 both groups' networks had an increased number of vertices and links compared to period 0. During period 0, the majority of vertices in the case network were connected in 1 large component versus 11 components in the control network due to fewer connected vertices. During period 1, each group's network had a majority of their vertices connected in 1 big component.

"case" for this study. The patients included in the study ranged in age from 18 to 103 years, with a median age of 72 years, and were equally distributed between the sexes. The largest proportion of cases were admitted at Campus A (48%), followed by Campus B (38%) and Campus C (14%). Patients stayed a median of 11 days in the hospital, although cases spent significantly less time in the ICU than did controls. About 8% of patients died in the hospital, which was similar between cases and controls, as were the proportions of ICU deaths (Table 1).

Figures 1a and 1b illustrate strikingly high numbers of links with certain rooms such as J2IC and E2NO (which are intensive care and neurologic observation units). In the MRSA pre-outbreak case network at Campus A, cases were clustered around the room J2IC (an ICU room), but this clustering was absent in the controls' network, which was divided into 11 separate components with no links to any other rooms or roommates. The MRSA case network at Campus A during period 0 was more connected, had more links, and had 1 large component compared to the control network in the same period.

Table 1
Characteristics of patients admitted to The Ottawa Hospital during the period of April 1, 2013, to March 31, 2014

Variable	Cases (n = 547)	Controls (n = 547)	Total (n = 1,094)	*P* value
Patient age at admission, median (IQR)	72.00 (57.00-83.00)	72.00 (56.00-83.00)	—	.93
Campus, n (%)				1
Campus A	263 (48.1)	263 (48.1)	526	
Campus B	209 (38.2)	209 (38.2)	418	
Campus C	75 (13.7)	75 (13.7)	150	
Patient gender, n (%)				1
Female	263 (48.1)	263 (48.1)	526	
Male	284 (51.9)	284 (51.9)	568	
Charlson comorbidity, median (IQR)	2.00 (0.00-3.00)	2.00 (0.00-3.00)	—	.73
Number of deaths,* n (%)	55 (10.0)	38 (6.95)	547	.06
			547	
Number of ICU deaths,* n (%)	17 (25.75)	6 (20)	66	.54
			30	
Number of ICU days, median (IQR)	6.00 (2.00-11.00)	14.00 (4.00-18.00)	—	**.04****
Length of hospital stay, median (IQR)	11.00 (4.00-25.00)	10.00 (5.00-21.00)	—	0.66

ICU, intensive care unit; *IQR*, interquartile range.
*Deaths refer to all-cause mortality during the enrollment hospitalization.
**The MRSA cases spent significantly less time in the ICU compared to controls.

Table 2
Overall structure network measures changes for MRSA cases and controls at The Ottawa Hospital campuses during reference periods

	Campus A			Campus B			Campus C		
	Period 0	Period 1	Percent (%)	Period 0	Period 1	Percent (%)	Period 0	Period 1	Percent (%)
Cases									
Vertices	911	1165	28	210	338	61	211	335	59
Links	2856	4074	43	445	752	69	605	1500	148
Density	0.054	0.036	−33	0.049	0.038	−22	0.130	0.107	−18
Component(s)	2	5	—	9	8	—	1	1	—
Controls									
Vertices	409	1646	302	190	406	114	314	379	21
Links	713	5165	624	353	893	153	999	1538	54
Density	0.030	0.025	−16	0.055	0.035	−36	0.084	0.095	13
Component(s)	11	5	—	3	3	—	1	1	—

NOTE: A vertex is the smallest unit of a network (eg, MRSA case or a control, attending physician, hospital room). A link is a relationship between 2 vertices in a network (eg, MRSA case room, control room, roommate room, MRSA case attending physician, control attending physician). Density is the number of lines in a simple network, expressed as a proportion of the maximum possible number of lines. A component is a portion of the network in which all vertices are connected, directly or indirectly, by at least 1 line.
MRSA, methicillin-resistant *Staphylococcus aureus*.

Substantially more clustering around J2IC and E2NO is visible for both cases and controls during the outbreak period (Fig. 1c and 1d), as it is the significant increase in numbers of links that join the controls into 1 large component.

After visualizing the networks, we calculated the network measures. The number of vertices representing the MRSA cases, controls, rooms, and attending physicians increased by 28%, 61%, and 59% at Campuses A, B, and C, respectively, from period 0 before the outbreak to period 1. Similarly, the number of lines or connections between the vertices also increased by 43%, 69%, and 148% for the 3 campuses during the same period. However, the density of the network decreased from period 0 to 1 in both groups, except for the Campus C control group, where it rose slightly by 13% (Table 2).

To ascertain if the network structures of the cases and controls were similar, consistent with the demographic and clinical data, we compared their degree measures during pre-outbreak and outbreak periods. There were no differences between the median degree centralities of cases and controls in period 0 at all 3 campuses (Table 3); however, during the outbreaks, controls had significantly higher median degree centrality than cases at Campus A ($P = .001$) and Campus B ($P = .02$), with no difference at Campus C ($P = .86$.)

The number of vertices (people and rooms) and links increased from period 0 to period 1 for both groups at all 3 campuses (Fig. 1a and 1b; Table 2), reflecting true rises in the numbers of cases, which then resulted in higher numbers of affected rooms and exposed roommates throughout the campuses. There was a significant increase in median degree centrality from period 0 to period 1 for both cases and controls in accordance with increased exposures and activity in rooms, except at Campus C (Table 4).

To elucidate possible routes of MRSA transmission, we made a timed, animated movie[40] of the MRSA case network at Campus C during the 2 reference periods (data can be provided upon request). We chose this particular network because it had the lowest number of vertices and links compared to case networks from the other campuses which resulted in a clear animation. Although we had data on patient rooms for every day, we used 2-week time frames, displaying the evolution of new vertices and new links as patients were moved from room to room. Each MRSA case is represented by a red or pink triangle (pink for cases with prolonged hospital stays followed from admission to discharge, and red for the other cases). Each roommate is represented by a green circle. For patient rooms, light blue squares represent the rooms followed from first to last time frame in the movie, and dark blue squares represent rooms that were transient. Finally, the attending physician is represented by a purple diamond. To further explain the animation, we extracted information on times of room occupancy from the more specific timed data that we had to give more exact exposures.

Initially, we examined Case 43, located in room H1CA in Cardiac Care Unit A, who tested MRSA positive 1 week after his hospital admission and 4 weeks before the outbreak occurred. Case 58 was admitted to the same room, H1CA, 1 week after Case 43, where they both spent 3 days, after which, 10 days later, Case 58 tested MRSA positive. After that, Case 58 was moved to different rooms: Cardiac Surgery ICU A (HCSA) for 1 day, Cardiac Surgery ICU B (HCSB) for 10 days, room 3301 for 13 days, H3 hallway for 8 minutes, room 3327

Table 3
Median degree centrality of cases and controls, by reference period and campus

Campus A	Median degree centrality*	
	Period 0 (n = 36)	Period 1 (n = 57)
Cases	5	6
Controls	6	16
P (Wilcoxon)	.74	.001
Campus B	**Period 0 (n = 18)**	**Period 1 (n = 38)**
Cases	6.5	5
Controls	8	9
P (Wilcoxon)	.26	.02
Campus C	**Period 0 (n = 7)**	**Period 1 (n = 25)**
Cases	29	29
Controls	39	28
P (Wilcoxon)	.20	.86

*Degree centrality is a centrality measure defined by the number of direct connections (links) each vertex had with other vertices.

Table 4
Median degree centrality compared between reference periods for cases and controls by campus

	Median degree centrality*		*P* value (Wilcoxon)
	Period 0	Period 1	
Campus A			
Cases (n = 36)	5	19	.001
Controls (n = 45)	5	20	<.0001
Campus B			
Cases (n = 19)	6	11	.03
Controls (n = 18)	8	18.5	.001
Campus C			
Cases (n = 7)	29	60	.20
Controls (n = 19)	28	32	.29

*Degree centrality is a centrality measure defined by the number of direct connections (links) each vertex had with other vertices.

for 30 days, HCSB for 3 days, and finally to room 3322 for 9 days, from which the patient was discharged home. Case 58 tested MRSA positive 10 days after sharing a room with Case 43 and was then moved to several different rooms. Unless tested promptly after colonization and/or infection and then effectively treated, this patient could have spread the infection further. Despite the availability of private rooms, Case 58 accumulated a number of roommates and, after being isolated for a period of time, appeared back in the main network connected to HCSB. Finally, both of these MRSA cases were discharged home, but many, if not all, of the subsequent MRSA cases were connected to rooms H1CA, HCSA, and HCSB, indicating one possible transmission route.

DISCUSSION

We conducted a case-control study of patients with MRSA and controls matched on sex, age, and campus in a large tertiary care facility in Canada. There were no demographic or clinical differences in the factors we measured between cases and controls that could influence risk of disease. The number of days in the ICU did differ, but this is to be expected when the cases were highly clustered around that ward, the reasons for which are addressed below. Then we linked the rooms, roommates, and attending physicians of cases and controls over time to construct a health care network. We did not detect any differences in median number of linkages for cases and controls nor rooms and roommates for all 3 campuses in the pre-outbreak period. This suggests that the 2 groups of patients were similar in both individual characteristics and in number of contacts or structural (hub) position on potential MRSA transmission routes under normal conditions.

We used epidemiological methods to identify outbreaks, and, because we had the timing of MRSA-positive tests over time, we illustrated potential transmission routes in a diagram of cumulative links during the pre-outbreak and outbreak periods at all 3 campuses. The MRSA case network at Campus A during period 0 was more connected, had more links, and had 1 large component compared to the control network in the same period. This is due to the fact that cases may have been connected to more rooms and roommates just prior to being identified with MRSA, which is also an indicator of possible subsequent transmission route to MRSA-negative roommates. This is not as obvious in the graphs from Campus B and Campus C (data can be provided upon request). Reasons for the clustering around an ICU include patient care related to MRSA itself and severity of illness. It is also likely that cases had more exposures to roommates and rooms in general; hence, they were more likely to be exposed to a contaminated room or MRSA-colonized roommate or health care workers. It is also possible that immediately before diagnosis the patient may have had increased contact with various health care workers, including physicians, in an attempt to diagnose his/her disease.

The case-control design is intended to show meaningful differences in the probability of possible causal risk factors between people who have and those who do not have the disease.[41] We conducted a traditional epidemiological study that confirmed that cases and controls were very similar. When we supplemented this with a health care network, we revealed possible exposures that were truly causative, such as hospital stays in rooms J21C (Fig 1) and H1CA. To investigate this further, we created a timed animation of cases occupying rooms on a smaller campus before and during an outbreak. After cases occupied a room, other cases arose from the same room, suggesting that the room or roommates were the sources of the organism. This echoes previous work on an outbreak of gonorrhea in which places of sex partner recruitment were added to a standard case-control study questionnaire, revealing that the only difference in the characteristics and sex behavior of cases and controls was attendance at a bar whose patrons had a high risk of gonorrhea and were sexually interconnected.[26]

Social network analysis was previously used successfully to enhance the investigation of a tuberculosis outbreak.[15] We have furthered that work here by using a case-control design, adding data on rooms instead of whole buildings and using data on the timing of MRSA acquisition to better capture person-to-person and environmental exposures.

Visible increases in the number of vertices and links of the case and control networks in the outbreak periods at all TOH campuses are evident (Fig 1), due to increasing numbers of cases, higher numbers of rooms occupied by cases, and removing roommates to isolate cases as a routine practice. However, moving roommates out of rooms occupied by cases may have spread the infection throughout the institution unless they were promptly tested and treated. Accordingly, the density decreased due to the limited number of connections each vertex can have, such as numbers of roommates per room and/or the amount of physical contact between patients and health care workers. Decreasing density relative to increasing vertices is well recognized in network theory as a function of limited time and space.[35] The decrease in the cases' degree centrality at Campus A and Campus B during the outbreak was also due to the routine isolation of cases, drastically reducing their number of connections with other people. Campus C is a smaller facility with many private rooms, so the number of connections with other patients and/or patient movement to other rooms limited the spread of infection initially and during the outbreak. This serves as an ideal example of the mechanism by which private and semi-private rooms can reduce the spread of MRSA.

Degree centrality indicated the most influential people and places in MRSA transmission that had the highest number of connections and were most likely to transmit MRSA. Places such as the ICU had the highest degree centrality (range, 128-2,456), followed by MRSA cases (range, 2-857). Cases with over 100 days of hospital days had higher number of connections compared to patients with fewer days of hospital stay. Attending physicians had the lowest degree centrality (range, 1-7), although they bridged different parts of the networks. Rooms with high degree centrality render institutions vulnerable to MRSA, as they may amplify transmission from only one person through contaminated doors, telephones, computer equipment, light switches, and other shared items concentrated in such a small, closed space containing so many people. As above, the rooms at Campus A in which the highest number of controls and their roommates had stayed prior to the outbreak differed from those in which MRSA cases had stayed. However, during the outbreak period they were the same, indicating that isolating cases in new rooms resulted in moving more people through those very rooms vacated by cases.

Limitations of this study include collecting contact information from other health care workers such as resident physicians, nurses, other HCWs (eg, diagnostic imaging technicians, respiratory therapists) currently not available in TOHDW, and patient transfer data between the 3 campuses of TOH, which are also vitally important. We also were not able to show in our networks if a roommate who came in contact with a case subsequently became a case, which we can avoid by using density sampling in the future. Finally, our data lacked information on shared equipment and its potential as a vector for transmission.

CONCLUSIONS

We have shown that SNA is a useful tool in understanding the transmission of MRSA in a hospital setting and may be the only way in which specific sources can be identified for inclusion into a case-control study of exposure and infection. Hospital infection control

programs may focus prevention efforts on patients with long hospital stays, on those who have had many room changes, and on "popular" places to enhance existing measures. In addition, more sensitive surveillance for MRSA that includes the entire institution and prompt molecular typing of each MRSA isolate at the start of an outbreak may provide more accurate data on MRSA sources.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.ajic.2019.05.026.

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