Network Analysis of Methicillin-Resistant *Staphylococcus aureus* Spread in a Large Tertiary Care Facility

Ioana Doina Moldovan

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School of Epidemiology, Public Health and Preventive Medicine

Faculty of Medicine
University of Ottawa

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Abstract

Statement of problem: Methicillin-resistant *Staphylococcus aureus* (MRSA) is an antibiotic-resistant bacterium of epidemiologic importance in Canadian healthcare facilities. The contact between MRSA colonized or infected patients with other patients, healthcare workers (HCWs) and/or the healthcare environment can result in MRSA transmission and healthcare-associated MRSA (HA-MRSA) infections in hospitals. These HA-MRSA infections are linked with increased length of hospital stay, economic burden, morbidity and mortality. Although infection prevention and control programs initiated in 2009 in Canada and other developed countries (e.g., UK, France, Belgium, Denmark, etc.) have been relatively successful in reducing the rate of HA-MRSA infections, they continue to pose a threat to patients, especially to the more vulnerable in long term care and geriatric institutions. Historically, MRSA was a problem mainly in hospital settings but after mid-1990s new strains of MRSA have been identified among people without healthcare-related risks and have been classified as community-associated MRSA (CA-MRSA). Furthermore, the distinction between HA-MRSA and CA-MRSA strains is gradually waning due to both the introduction of HA-MRSA in communities, and the emergence of CA-MRSA strains in hospitals.

The purpose of this thesis was to explore the feasibility of constructing healthcare networks to evaluate the role of healthcare providers (e.g., physicians) and places (e.g., patient rooms) in the transmission of MRSA in a large tertiary care facility.

Method of investigation: a secondary data case-control study, using individual characteristics and network structure measures, conducted at The Ottawa Hospital (TOH) between April 1st, 2013 and March 31th, 2014.

Results: It was feasible to build social networks in a large tertiary care facility based on electronic medical records data. The networks' size (represented by the number of vertices and lines) increased during the outbreak period (period 1) compared to the pre-outbreak period (period 0) for both groups and at all three TOH campuses. The calculated median degree centrality showed significant increase in value for both study groups during period 1 compared to period 0 for two of the TOH campuses (Civic and General). There was no significant difference between the median degree centrality calculated for each study group at the Heart Institute when compared for the two reference periods.

The median degree centrality of the MRSA case group for period 0 showed no significant difference when compared to the same measure determined for the control group for all three TOH campuses. However, the median degree centrality calculated for period 1 was significantly increased for the control group compared to the MRSA case group for two TOH campuses (Civic and General) but showed no significant difference between the two groups from the Heart Institute. In addition, there was a correlation between the two network measures (degree centrality and eigenvector centrality) calculated to determine the most influential person or place in the MRSA case group networks. However, there was no correlation between the two network's measures calculated for physicians included in MRSA case group networks.

Conclusions: It is feasible to use social network analysis as an epidemiologic analysis tool to characterize the MRSA transmission in a hospital setting. The network's visible changes between the groups and reference periods were reflected by the network measures and supported also by known hospital patient movements after the outbreak onset. Furthermore, we were able to identify potential source cases and places just prior of the outbreak start. Unfortunately, we were not able to show the role of healthcare workers in MRSA transmission in a hospital setting due to limitations in data collection and network measure chosen (eigenvector centrality). Further research is required to confirm these study findings.

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1.1   Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA), one of the most common causes of healthcare-associated infections in Canada spreads between people by direct contact, shared items or by contact with contaminated surfaces. Historically, MRSA has been a healthcare acquired pathogen. The MRSA control in hospitals has been important because of the severity of infection among vulnerable patients and the limited antibiotics available for treatment. While MRSA infection rates have been decreasing since 2009 in Canada, especially in hospital settings, MRSA still remains a significant cause of infection.[12] The actual infection rates continue to surpass those observed in early 2000s.[12] For example, in 2014, the MRSA infection incidence rate was 2.08 cases per 1,000 patient admissions and 2.83 cases per 10,000 patient-days compared to 1.13 cases per 1,000 patient admissions and 1.4 cases per 10,000 patient-days in 2001.[8, 77] Similar trends have been observed in other developed countries. [12] Furthermore, MRSA infection is associated with increased morbidity, mortality and healthcare costs .[15]

In 2010, in Canada, it was estimated that 4.2% of hospitalized patients became infected or colonized with MRSA resulting in an annual hospital cost of about $36.3 million.[13, 14]In a report published by the Public Health Agency of Canada, in 2012 approximately 9% of patients with a non-bloodstream MRSA infection died and 25% of patients with an MRSA bloodstream infection died at 30 days after the date of positive culture. [1]

With changing trends in healthcare delivery resulting in the provision of complex treatments outside of acute healthcare facilities (e.g., ambulatory care, physician office and home settings), there is an increased need for infection prevention and control measures outside of hospital settings.

The overall goal of this thesis is to examine the feasibility of building healthcare networks in a large tertiary care setting (using network analysis methods), and then based on calculated network measures to evaluate the role of healthcare workers and places (as part of this social network) in the transmission of MRSA.

1.2   Study Objectives

The primary objective of this study was to assess the feasibility of constructing healthcare networks in a hospital setting by using electronic medical record data (from The Ottawa Hospital Data Warehouse and The Ottawa Hospital Infection Prevention and Control Program), and social network analysis.

The secondary objective was to determine the network structure measures (e.g., centrality, density) and use these measures to evaluate the role of healthcare workers (HCWs) and places (e.g., patient rooms) in the transmission of MRSA in a large tertiary care facility. [*]

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[*] **Note:** on the initial thesis proposal submitted to the University of Ottawa there was a third objective for this project: to evaluate whether the networks generated by The Ottawa Hospital (TOH) data resemble actual MRSA stain specific transmission. This objective was impossible to complete as it was discovered after the submission of the thesis proposal that MRSA strain data was not available.

Chapter 2 - Background

2.1   MRSA

Methicillin - resistant *Staphylococcus aureus* (MRSA) is a virulent *Staphylococcus aureus* (*S. aureus*) strain, cross-resistant to beta-lactam antibiotics (e.g., methicillin, cloxacillin/oxacillin, cephalosporins) and with heterogeneous resistance to non-beta lactam antibiotics (e.g., aminoglycosides, macrolides, clindamycin, tetracyclines, quinolones).[1] *S. aureus* is a common bacterium of the human's normal flora which asymptomatically colonises approximately one third of the human population, and is considered one of the most frequently encountered causes of bacterial infection in humans. [2, 3] Methicillin resistance in *S. aureus* was first isolated in 1961 shortly after the introduction in clinical use of the semisynthetic penicillinase-resistant penicillins (e.g., methicillin). [1, 4] While the majority of patients from whom MRSA is isolated are colonized (they are asymptomatic and do not have any evidence of infection), it is well recognized that colonization generally precedes the development of infection.

MRSA is a pathogen of epidemiologic importance due to its resistance to many first line antibiotics and reported association with increased morbidity and mortality compared with susceptible *S. aureus* strains. As a result, many healthcare facilities have implemented specific measures to limit the spread of MRSA among patients.

Until mid-1990s MRSA was considered almost exclusively a healthcare associated pathogen (HA-MRSA). [1, 2, 5, 6] Since then, new strains of MRSA have been identified among people without healthcare-related risks and these have been classified as community-associated MRSA (CA-MRSA). [1, 2, 5, 6] CA-MRSA, the result of a clonal dissemination of MRSA, is genetically distinct from HA-MRSA (having unique virulence genes and factors not present in HA-MRSA strains). [1, 7, 8]

2.1.1 *Healthcare-associated methicillin-resistant Staphylococcus aureus (HA-MRSA)*

The Canadian Nosocomial Infection Surveillance Program (CNISP), a collaborative effort of the Public Health Agency's (PHAC) Centre for Communicable Disease and Infection Control (CCDIC), the National Microbiology Laboratory (NML), and sentinel hospitals across Canada (as per PHAC, in 2015 there were 62 sentinel hospitals in 10 provinces) which participate as members of the Canadian Hospital Epidemiology Committee (CHEC), a subcommittee of the Association of the Medical Microbiology and Infectious Disease (AMMI) Canada, has been conducting surveillance in Canadian acute-care hospitals for more than 20 years. TOH is part of the CNISP network of hospitals.

In 2014, CNISP used the following case definition for HA-MRSA:

- "isolation of *Staphylococcus aureus* from any body site

  AND

- resistance of isolate to oxacillin

  AND

- patient must be admitted to the hospital

  AND

- is a "newly identified MRSA case" at a Canadian Hospital Epidemiology Committee (CHEC) facility at the time of hospital admission or identified during hospitalization.

  This includes:

  - MRSA cases identified for the first time during this hospital admission
  - Cases that have been previously identified at other non-CHEC sites (since we want newly identified MRSA cases at CHEC sites)
  - Cases that have already been identified at the current site but are new cases. This can only be identified if the previously identified case has another strain.

MRSA surveillance exclusion criteria:

- MRSA cases previously identified at other CHEC sites

- Emergency, clinic, or other outpatient cases

- Cases re-admitted with MRSA (unless it is a different strain)

Healthcare-associated (HA) *case* definition: Once the patient has been identified with MRSA, he/she will be classified as HA based on an assessment of the practitioner using the following criteria:

- Exposure to any healthcare setting (including long-term care facilities or clinics) in the previous 12 months

  OR

- Has been hospitalized for greater than 48 hours" [8]

HA-MRSA can be present in people with one or more of the following healthcare-related risk factors: previous history of MRSA infection or colonization, history of surgery, hospitalization (e.g., due to chronic medical conditions), receipt of antibiotic therapy within 3 months, presence of an invasive device at the time of admission, dialysis, older age, or residence in a long-term facility in the previous 12 months prior to culture date.[2] Over the past two decades, due to major changes in the healthcare delivery system (e.g., treatment shift of more acute illnesses to outpatient care, homecare and long-term care facilities), patients with MRSA have been discharged into the community where spread may have occurred. In addition, with the continuing changing epidemiology of MRSA and the emergence of MRSA outside of healthcare settings, it is becoming more difficult to classify MRSA as strictly healthcare-associated or community-associated.[2]

HA-MRSA is the cause of many healthcare-associated infections (HAIs) including surgical site infections (SSIs), ventilator associated pneumonias (VAPs), central line-associated bloodstream infections(CLABSIs), catheter-associated urinary tract infections(CAUTIs) and wound infections.[2] In Canadian acute-care hospitals, between 2008-2012, CLABSIs accounted for over one-quarter of the total MRSA bloodstream infections.[15] Furthermore, during the same surveillance period, 9% of patients with non-bloodstream MRSA infection (e.g., surgical site, respiratory, etc.) died and 25% of patients with a bloodstream infection (BSI) died at 30 days after the date of the positive culture. [15]

2.1.2   Community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA)

As per the Public Health Agency of Canada, Antimicrobial Resistant Organisms (ARO) Surveillance - Surveillance Report for data from January 1, 2009 to December 31, 2014, a community-associated case is defined as follows**:**

- "Has been hospitalized for less than 48 hours

  AND

- Has no previous history of the organism

  AND

- Has no prior hospital or long-term care admission in the past 12 months

  AND

- Has no reported use of medical devices"[8] (e.g., pacemakers and implantable cardiac defibrillators, hip and knee prosthetic joint, prosthetic heart valves, coronary stents, peripheral and central venous catheters, arterial catheters, etc.)

CA-MRSA strains have been associated with severe skin and soft tissue infections and necrotizing pneumonias, as well as BSI, otitis media and externa, and joint infections.[2] There are specific sub-populations with an increased risk for acquiring and spreading CA-MRSA including men who have sex with men [16,17], sports participants[18,19], military personnel[20], prisoners[21], children, household contacts of MRSA patients, Emergency Department patients, urban underserved communities, cystic fibrosis patients, people infected with human immunodeficiency virus, veterinarians, livestock handlers and pet owners.[22]

The proportion of MRSA infections identified as community-acquired MRSA (CA-MRSA) has steadily increased over time and by 2012 represented just under one-third of cases classified.[15] In addition, in 2013 19.9% of MRSA infections were from blood and 80.1% were from clinical sources other than blood.[12] Skin and soft tissue infections (SSTI) represented the largest proportion (43%) of MRSA infections identified from clinical sources other than blood.[12] Furthermore, the proportion of MRSA infections (all non-blood sources) identified as CA-MRSA has steadily increased from 25% in 2008 to 33% of cases in 2012.[12]

In Canada, during the period of 1995 to 2009, based on the data reported by the CNISP, the overall rate of MRSA in CNISP hospitals (in 2009, fifty Canadian hospitals in ten provinces reported data to CNISP) increased from 0.51cases/1,000 patient-admissions in 1995 to 9.5 cases/1,000 patient-admissions in 2009 (Figure 1).[1]

Figure 1: Overall MRSA rates, Canadian Nosocomial Infection Surveillance Program (CNISP) 1995-2009 (per 1,000 patient-admissions)
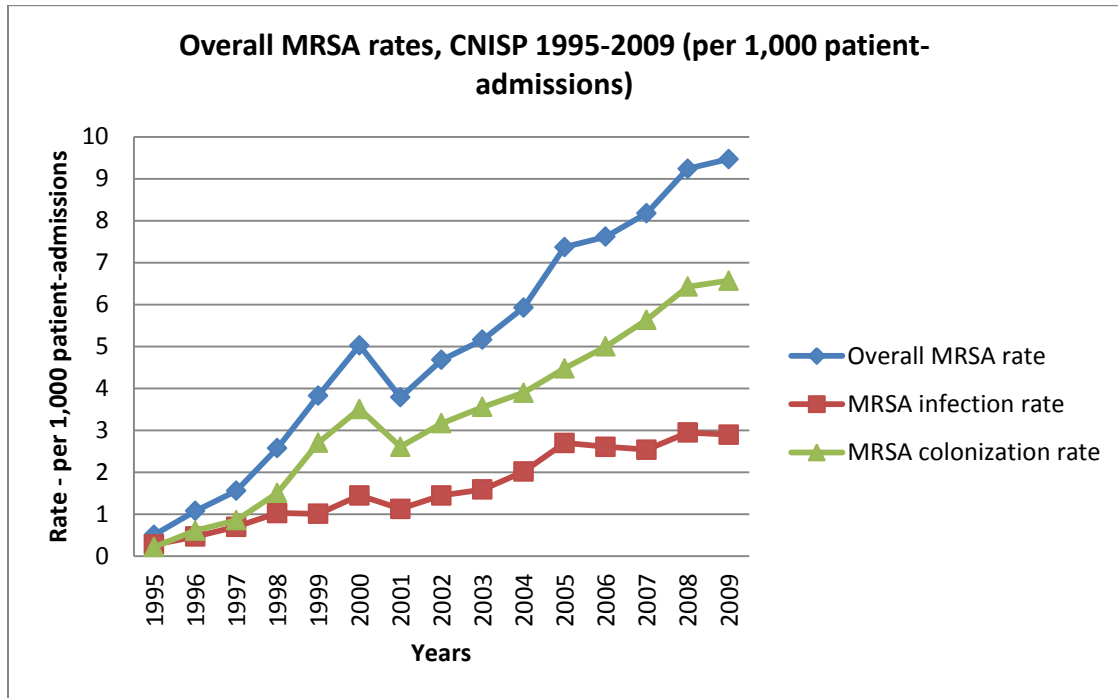
(Figure 1 was published by Public Health Agency of Canada, CNISP - Results of the surveillance of Methicillin resistant *Staphylococcus aureus*, from 1995 to 2009)

Most recent MRSA surveillance results released by Public Health Agency of Canada showed that the incidence of overall MRSA (infection and colonization) in Canada has decreased since 2009 from 9.45 to 7.63 cases/1,000 patient- admissions in 2014.[8] (see Figure 2)

Figure 2: Overall MRSA rates, Canadian Nosocomial Infection Surveillance Program (CNISP) 2009-2014 (per 1,000 patient-admissions)
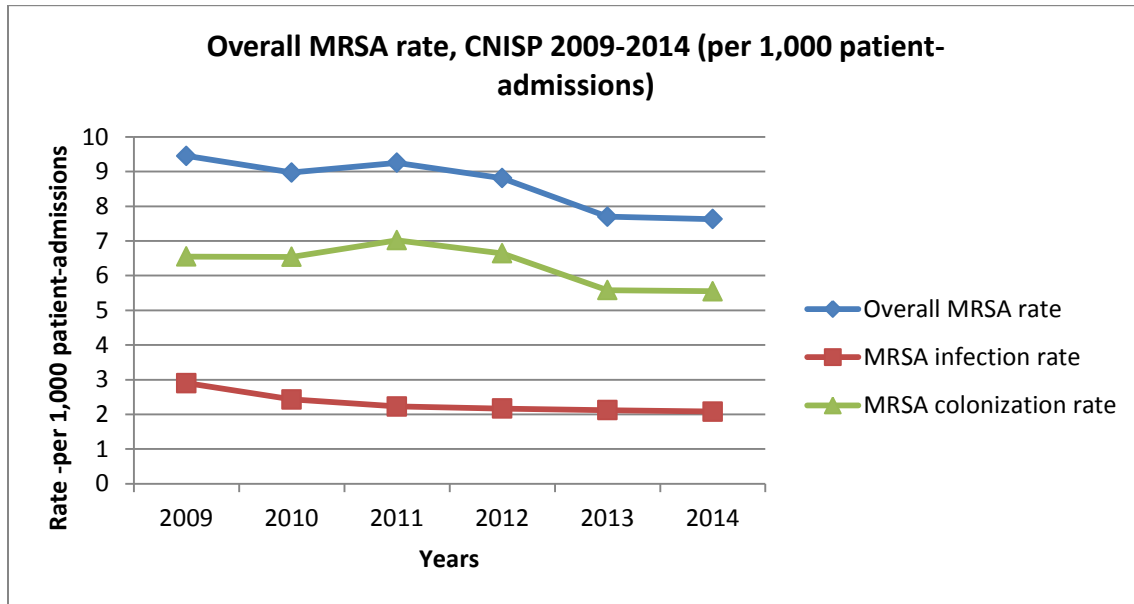
(Figure 2 was created based on data published by Public Health Agency of Canada - Antimicrobial Resistant Organisms (ARO) Surveillance: Summary Report for data from January 1, 2009 to December 31, 2014)

The "iceberg effect" refers to the relationship between the number of MRSA infected (the smallest visible portion of the iceberg), and the number of MRSA colonized cases (the largest, underwater, and not-visible portion of the iceberg)[23]. Therefore, it has been a challenge to calculate the true overall MRSA rates and especially MRSA colonization rates when it is almost impossible to know the real number of MRSA colonized people. MRSA colonized people are asymptomatic, unaware of carrying the MRSA and their number is much higher compared to MRSA infected people.[23]

2.1.3   *Laboratory characterization of HA-MRSA and CA-MRSA genotypes*

Laboratory characterization has revealed distinct differences in the microbiological characteristics of CA-MRSA and HA-MRSA.[24, 25] In addition to the surveillance or clinical definition, both HA- and CA-MRSA are differentiated based on strain typing of isolates as described by McDougal et al (2003).[24] MRSA strains generally recognised as CA-MRSA include CMRSA7 (USA400, ST1, CC1) and CMRSA10 (USA300, ST8, CC8).[16, 24, 25] HA-MRSA strains are generally accepted as CMRSA1 (USA600, ST4, CC45), CMRSA2 (USA100, USA800, ST5, CC5), CMRSA3/6 (ST241 or ST239), CMRSA4 (USA200, ST36), and CMRSA5 (USA500, ST1, CC1).[16, 24, 25]

Based on CNISP data, from 1995 to 2007, a total of 13,648 (37%) of MRSA isolates were typed by using pulse-field gel electrophoresis (PFGE) (9). The majority of strains were characterized as HA-MRSA strains. Overall, the most common strain type identified was CMRSA-2 representing 47% of the typed strains, followed by CMRSA-1 with 19% of the typed strains. CA-MRSA genotypes were represented by CMRSA-10 and CMRSA-7 accounting for 9%, respectively 2% of the typed strains (Figure 3).[16]

Figure 3. Overall Canadian MRSA Strains Identified in the Canadian Nosocomial Infection Surveillance Program, 1995–2007
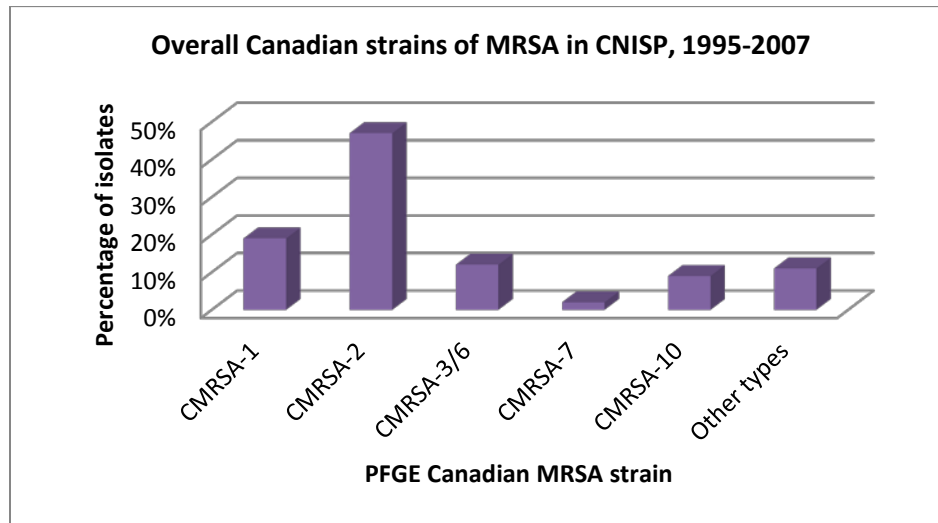
(Figure 3 was created based on data published by Simor AE, Gilbert NL, Gravel D, Mulvey MR, Bryce E, Loeb M, Matlow A, McGeer A, Louie L, Campbell J in Canadian Nosocomial Infection Surveillance Program. Methicillin-resistant Staphylococcus aureus colonization and infection in Canada: National Surveillance and Changing Epidemiology, 1995-2007)

However, it is important to note the change in the predominant strain type.[16] At the beginning of the surveillance period, CMRSA-1 represented 40% of the strain types, but by 2007 it almost completely disappeared and was replaced by CMRSA-2, another HA strain type.[16] In addition, between 1995 and 2010 the proportion of CA-MRSA strains increased from 2% to 25% .[10] From 1995-1999, CA-MRSA strains were rarely documented in CNISP hospitals, but between 2004 and 2007 the CMRSA-10 strain was reported as the second most common MRSA strain type (17% of isolates typed) (Figure 4).[16]

Figure 4. Change of the predominant Canadian pulse-field gel electrophoresis MRSA isolates, identified in CNISP, during 1995-2007

Canadian PFGE MRSA isolates identified by CNISP, 1995-2007
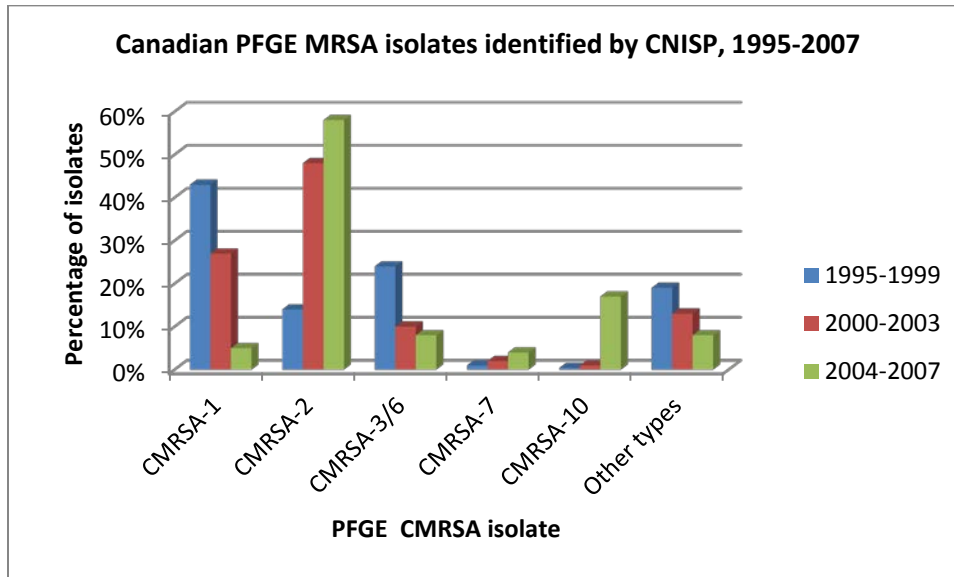
(Figure 4 was created based on data published by Simor AE, Gilbert NL, Gravel D, Mulvey MR, Bryce E, Loeb M, Matlow A, McGeer A, Louie L, Campbell J in Canadian Nosocomial Infection Surveillance Program. Methicillin-resistant Staphylococcus aureus colonization and infection in Canada: National Surveillance and Changing Epidemiology, 1995-2007)

Furthermore, as per Nichol et al (2013)[7], between 2007 and 2011 among 5443 *S. aureus* isolates submitted to the CANWARD study (a national surveillance study assessing pathogen prevalence and antimicrobial resistance in Canadian hospitals) there were 1266 isolates identified as MRSA (23.3%).[7]

The MRSA isolates were characterised by sequence-based typing of the staphylococcal protein A (*spa*) gene, and then the Canadian epidemic PFGE strain type were inferred from the observed *spa* type.[7]

Of the 1266 MRSA isolates identified, 868 (68.6%) were characterised HA-MRSA, and 366 (28.9%) as CA-MRSA.[7]

As shown in Figure 5, between 2007 and 2011 in Canadian hospitals, the predominant epidemic strain type was CMRSA-2 accounting for 58.1% of all MRSA isolates and 84.8% of HA-MRSA genotypes.[7] As

well, among HA-MRSA isolates the proportion of CMRSA-3/6 isolates decreased over time from 10.6% in 2007 to 0.6% in 2011.[7] On the other hand, the CA-MRSA strain type CMRSA-7 and CMRSA-10 represented 6.8% and 22.1% of all MRSA isolates identified.[7] Between 2007 and 2011, CMRSA-10, the second most commonly identified epidemic type overall, increased significantly from 13.2% to 28.6% (Figure 5).[7]

Figure 5. Molecular characterization of CA-MRSA and HA-MRSA genotypes in Canadian Hospitals between 2007 and 2011
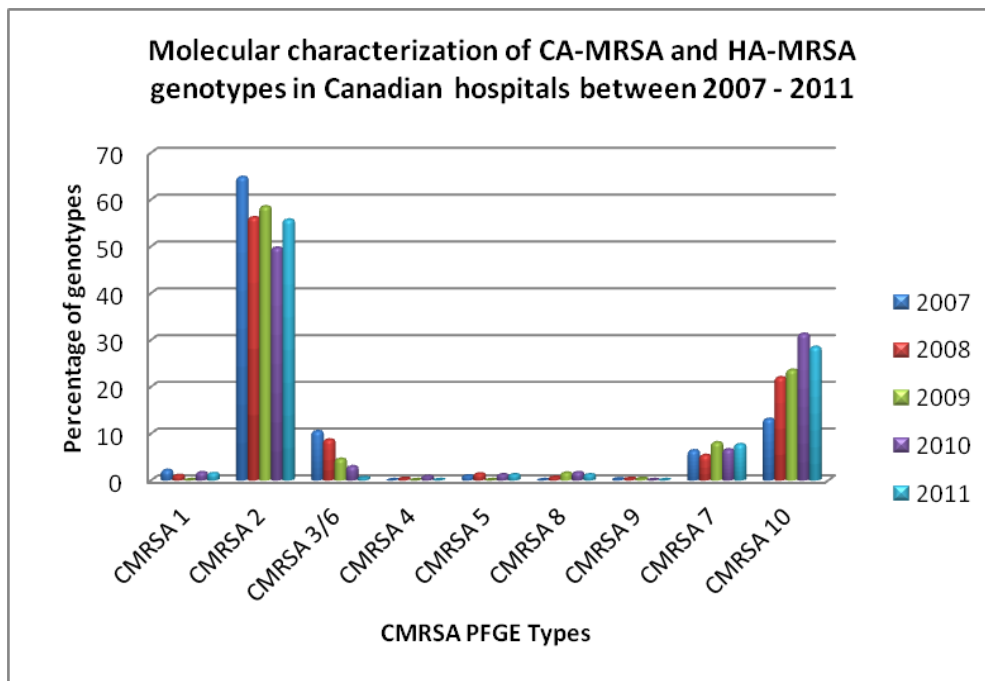
(Figure 5 was created based on data published by Nichol KA, Adam HJ, Roscoe DL, Golding GR, Lagacé-Wiens PR, Hoban DJ, Zhanel GG; Canadian Antimicrobial Resistance Alliance in Changing epidemiology of methicillin-resistant Staphylococcus aureus in Canada. *J Antimicrob Chemother*. 2013 May; 68 Suppl 1: i47- i55)

2.1.4   Reservoirs for MRSA transmission

The reservoirs for MRSA transmission in healthcare facilities (acute care, long term care and rehabilitation facilities) consist of MRSA colonized and infected patients, healthcare workers (e.g., attending physicians, residents, nurses, x-ray technicians, etc.), environmental surfaces, medical

equipment in the rooms of MRSA colonized or infected patients, hospital rooms where these patients receive specialised services (e.g., ultrasound, physiotherapy , x-ray rooms, etc.) and possibly household contacts of patients colonized or infected with MRSA.[2]

2.1.4.1   MRSA Reservoirs in Acute-Care Facilities

Patients who are colonized or infected with MRSA in a community setting or a healthcare facility are the major reservoirs of MRSA in the hospital setting.

It is important to mention that the true prevalence of MRSA among hospitalised patients is not known and varies among acute-care hospitals.[2] For example, most of US hospitals are not using active surveillance testing to identify MRSA colonized patients.[26] Furthermore, in 2007, a study by Salgado et Farr demonstrated that between February 1988 and November 2002, clinical cultures alone identified just 15% of the MRSA colonized patients identified during the hospital admission by active surveillance cultures.[26]

Environmental Surface and Medical Equipment contamination with MRSA is common in rooms occupied by MRSA colonized or infected patients.[2] It is well known that MRSA survives for relatively long periods of time in the environment and is resistant to desiccation.[27, 28] For example, one study found that MRSA survived up to 11 days on plastic charts and for 21 days on laminated tabletops.[29] Based on numerous studies, MRSA was able to contaminate various inanimate objects such as mattresses, bed linen, patient gowns, nurse's uniform, doctor's ties, tourniquets, pens, televisions, remote controls, blood pressure cuffs, infusion pumps, stethoscopes, telephones, as well as touch surfaces such as bed rails, floors, overbed tables, bed frames, bed raising panels, door handles, sinks, taps, computer key boards, bedside chairs, and light switches.[2]

Healthcare Workers (HCWs) who may be transiently colonized with MRSA constitute additional potential reservoirs for MRSA transmission.[2] Albrich and Harbarth (2008) reviewed data from 127 published studies and determined that the average MRSA prevalence among HCWs was 4.6% (95% CI, 1.0% - 8.2%).[30] Furthermore, in these reviewed studies, the prevalence of MRSA among HCWs varied from 0% to 59% as a result of differences in settings in which HCWs' screening occurred (e.g., end vs. beginning of shift), the HCWs' occupation, study year and the method of screening. [30] In addition, 5% of MRSA-colonized HCWs described in the reviewed studies had developed an MRSA infection, most frequently a skin and soft tissues infection.[30] The risk factors associated with MRSA carriage among HCWs include: chronic skin diseases, recent antibiotic use, poor hand hygiene practices, high work load, close contact with patients, and working in an hospital area with high MRSA prevalence among patients.[30]

2.1.4.2   MRSA reservoirs in Long-term care and Acute Rehabilitation Facilities (LTC&ARFs)

LTC&ARFs have a higher prevalence of MRSA among their residents compared to patients of acute-care hospitals.[2] This may be due to various patient risk factors for MRSA (e.g., older age, chronic illnesses, numerous hospital admissions), and been transferred from acute-care hospitals.[2]

2.1.4.3   MRSA reservoirs in household environments

Household environments include the homes of MRSA carriers.[2] MRSA was recovered from surfaces and items within these households including sinks, tubs, countertops, faucet handles in kitchens and bathrooms, dish sponges and towels, pet food dishes, infant high-chair trays, etc.[2, 31]

Schools, daycare centers and athletic facilities also play an important role in perpetuating the spread of CA-MRSA among households. For example, in athletic facilities, CA-MRSA has been isolated on water coolers, treatment tables, locker room shower handles, sink faucet handlers, and as well it has been identified as cause of invasive HA-MRSA infections.[2, 32]

Close personal contact with MRSA colonized or infected patients results in MRSA acquisition by household contacts who provide healthcare and have prolonged exposure to these patients.[2]

Animal Reservoir, including companion animals/household pets, and animals visiting healthcare facilities, may contribute to the MRSA transmission to humans since pet therapy and personal pet visitation are now common practices in healthcare facilities.[2]

2.1.5 Transmission of MRSA strains

MRSA patient hand carriage represents an important factor that may affect the amount of environmental MRSA contamination.[2] Once the environment is contaminated with MRSA, this can be transiently transferred to the HCWs' hands and clothing when they have direct patient contact or touch contaminated surfaces in the patient's room. As a result, the HCWs can then become vectors for MRSA transmission to other patients or staff.[2] In addition, other hospitalized patients may acquire MRSA from contact with contaminated objects, medical equipment, environmental surfaces or inhalation of aerosolized droplets from chronic nasal carriers.[2]

CA-MRSA strains are also most frequently transmitted by direct and close contact with a colonized/ infected patient or by contact with contaminated fomites used by an MRSA contaminated patient.[2]

In conclusion, the contact between MRSA colonized or infected patients with other patients, their HCWs or the healthcare environment can result in transmission of MRSA, and may lead to MRSA healthcare-associated infections. MRSA infections can appear sporadically or in the setting of a hospital outbreak and are associated with increased length of hospital stay, antibiotic resistance, increased morbidity and mortality, and increased healthcare costs (in Canada the direct healthcare costs attributable to MRSA alone averaged $82 million in 2004).[10]

2.2   *Social Network Analysis*

In this study, Social Network Analysis (SNA) was used to understand the underlying context and dynamics of MRSA transmission in a large tertiary acute-care hospital. It also helped to determine the influence that the connections between people (e.g., MRSA patients, roommates, HCWs,) and places (i.e., patient's room) have in the transmission of MRSA in a hospital setting.

The concept of "social network" was first introduced in 1954 by J.A. Barnes in an article of anthropology studying the social organization of a small Norwegian island parish through the various ways of interaction between the members of that society.[33] Barnes got his data by observation. He defined the concept of a "network" as a set of "points" some of them connected by "lines".[33] It was mentioned that the "points" represented people or groups of people, and the "lines" were the interactions between them.[33] Also, Barnes introduced the concept of "class network" as a network of social ties established between pairs of individuals based on kinship, friendship and acquaintance.[33] This class network analysis showed a hierarchical organisation of the administrative (e.g., administration of the parish) and industrial groups (e.g., fishing vessels, marketing cooperatives, herring-oil factories) even though the community members regarded each other as approximately socially equal.[33]

Four important characteristics of the SNA are that it: (1) provides methods to detects and interprets patterns of social connections between vertices (also named actors/nodes, see in Table 1- definition); (2) is based on empirical data; (3) is highly graphical and (4) uses mathematical and computational models.[34]
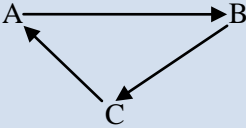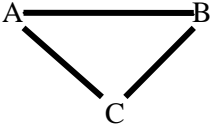
SNA has three main branches: (1) *network visualization*, (2) *network description* and (3) *new methods around stochastic and longitudinal network analysis*.[34, 35] In this thesis, *network visualization* and *network description* will be used as data analysis tools. *Network visualization* shows details on network structure and relationships in a graphic format, and is a major part of the SNA.[34, 35] *Network description* involves analyses to determine: (a) the position of individuals and /or places in the network (e.g., degree centrality), (b) properties of network subgroups (e.g., dyad, k-core, clique), or (c) characteristics of the entire network (e.g., density, centralization).[34]

2.2.1   Network Terms & Definitions

To better understand the SNA concepts used for data analysis in this thesis, first we need to enumerate the basic SNA terms and their definitions.

Table 1. Terminology and definitions commonly used in Social Network Analysis

Term	Definition
Network	A *network* is a set of vertices and a set of lines connecting pairs of vertices. A line linking two vertices represents a relationship between those vertices.
Graph	A *graph* is a drawing of a network
Vertex/Node/Actor	A *vertex* is the smallest unit of a network. It represents an individual, group, company, country, etc. (for example, in this thesis can be an MRSA case or control, a HCW, or a hospital room). (see Appendix A)
Line/Tie	A *line* represents a relationship between two vertices in a network (e.g. friendship, kinship). A *line* can be *directed* or *undirected*. A *directed line* is called an *arc* while an *undirected line* is an *edge*. (see Appendix A)

Arc	*An arc* is an ordered pair of vertices in which the first vertex is *the sender* (the tail of the arc) and the second is *the receiver* of the line (the head of the arc). *An arc* points from the sender to a receiver. In this example of sharing information, A share information with B. B share information with C who share information with A. We have a *directed* network, and the vertices are connected by *arcs*.
Edge	*An edge* has no direction, and is represented by an unordered pair. *An edge* is equivalent to a bidirectional arc since it does not matter which vertex is first or second in the pair. In this examples of sharing information, the connections between vertices are undirected, therefore we do not know who share information with whom. The information can be shared by either one of vertices in the pair. This is an *undirected* network and the vertices are linked by *edges*.
Component	A *component* is a portion of the network in which all vertices are connected, directly or indirectly, by at least one line. By definition, each **isolate** is a separate component. (see Appendix A)
Directed graph	A *directed graph* contains one or mare *arcs*.
Undirected graph	An *undirected graph* contains no arcs: all of its lines are *edges*.
Density	*Density* is the number of lines in a simple network, expressed as a proportion of the maximum possible number of lines. A complete network is a network with maximum density which is equivalent to - all my friends are friends with each other.
Adjacent	Two vertices are *adjacent* if they are connected by a line.
Degree	In a simple undirected network, the *degree* of a vertex is equal to the number of vertices adjacent to this vertex: its *neighbors*.
Ego	*Ego* is an individual "focal" vertex. *Ego* can be a person, groups, organization, etc. (see Appendix A)
Neighborhood	*Neighborhood* is a collection of *ego* and all vertices (*alters*) with whom the ego has a connection at some path length (one-step). It includes only ego and vertices that are directly adjacent. Also, it includes all the lines among all the vertices to whom the ego has a direct connection. (see Appendix A)
Degree Centrality	*Degree centrality*, a centrality measure, equals the number of ties that a vertex has with other vertices.[38] Generally, vertices with a higher degree or more connections are more central to the structure and tend to have a greater ability to influence others[38] (i.e., in our case to transmit the MRSA infection)
Eigenvector	*Eigenvector centrality*, a centrality measure, is based on the principle that the importance of a vertex depends on the importance of its neighbors. Therefore, a

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Centrality	vertex that has high eigenvector score is one that is adjacent to vertices that have themselves high scores. In other words, even if a vertex influences just one other vertex, which subsequently influences many other vertices (they influence still more others), then the first vertex in that chain is highly influential.
Geodesic path	Is the shortest-length path between a given pair of vertices
Dyad	A pair of vertices and the possible line between them
Triad	Three vertices and the lines among them

(Nooy W., Mrvar A. and Batagelj V. Exploratory Social Network Analysis with Pajek, *Cambridge University Press*, 2005;
Yan E. and Ding Y. Applying Centrality Measures to Impact Analysis: A Coauthorship Network Analysis, *Journal of the American Society for Information Science and Technology*, 60(10):2107-2118, 2009;
Borgatti S.P. Centrality and network flow, Social Networks 27 (2005) 55-71
Robert A. Hanneman and Mark Riddle. 2005. Introduction to social network methods. Riverside, CA: University of California, Riverside - published in digital form at http://faculty.ucr.edu./~hanneman/)

2.2.2   *Applying SNA in Epidemiology*

In Epidemiology, SNA has been used as a tool to investigate, explain and comprehend structural and relational aspects of social networks or subsets of networks.[34, 35] Using SNA as a method of analysis in Epidemiology can be explained by the relation of conditionality that exists between the transmission of a disease and the nature of interactions between an individual and his environment.[36] This means that existent relationships between people and/or places are sufficient to carry infection. On the contrary, no relationships between people and/or places mean no infection transmission. However, the infection transmission depends on the type of relationship, as well (e.g. direct contact, duration of contact). For example, in the case of a sexually transmitted disease (STD) the chances of an individual to catch the disease depends on the nature of the social contacts within his network.[36]

For over three decades social networks have been used as tools to analyse infection transmission. The first application of SNA in Epidemiology was a study on STDs by Klovdahl (1985) designed to better understand the spread of HIV. [37] Klovdahl used CDC data on personal relationships among 40 AIDS patients (19 initial patients diagnosed with AIDS from LA or Orange County, California, and 21 from their named sexual partners with AIDS as well, living in different parts of US) to build a social network. Using SNA, he proved that there were personal contacts (e.g. sexual relationships) between these people that could allow transmission of an infectious agent.[37] There were inconsistencies related to the temporal sequences of dates of symptom onset due to the difficulty in estimating the incubation period for this disease, at that time. This was followed by larger-scale studies performed in Winnipeg, Manitoba, Canada[38] and Colorado Springs, Colorado, USA [39] which continue to be important sources of information on human sexual networks and the potential transmission routes of sexually transmitted infections (STIs).[40] These studies were performed using SNA showing the importance of not just human connections but the environmental/geographic context(location/fomites) in the transmission of infectious agents (e.g., STI, tuberculosis, bloodborne pathogens diseases).[36, 41-45]

SNA of infection transmission in the healthcare setting has been used to a lesser extent. In several studies, dynamic network analysis has been used as a tool to model infection transmission and to determine the effectiveness of control measures in relation to influenza [46], *Mycoplasma pneumoniae* [47] and nosocomial infection.[48] In addition, a study of Geva A. et al (2011) using SNA showed that interactions among pediatric patients and HCWs influenced the transmission of MRSA in a neonatal intensive care unit of a large tertiary care facility.[49] Geva A. et al used electronic health records to identify the study participants and sibship information, MRSA surveillance cultures, patient room locations, nursing assignments and then, built patient- and unit-based networks.[49] After that, the study authors used multivariate models to quantify the risk of MRSA colonization of an uncolonized infant as result of exposure to his/her MRSA-colonized sibling. The study concluded that a MRSA-negative infant admitted in NICU at the same time

with a MRSA-positive infant had a higher odds of becoming MRSA-colonized if the colonized infant is his/her sibling (the siblings were left together during the hospital stay despite their MRSA colonization status, but an unrelated patient, if MRSA uncolonized, was separated from an MRSA colonized roommate).[49] As well, it was shown that sharing a nurse during hospital stay increased the odds of MRSA uncolonized patients of becoming colonized.

2.2.3   Brief overview of network analysis methods

SNA is a method that focuses on relationships between vertices (e.g., individuals, groups, organizations, countries) while traditional statistical analysis methods focus on the subject's attributes (e.g., variables). [34]

The advantages of using network analysis in Epidemiology are very well illustrated by Slattner et al (2011) in their "Social Network Analysis in Epidemiology: Current Trends and Perspectives" study. They noted that: (1) a network's structure provides valuable information on the dynamics of social contacts between individuals which is known to have a significant influence on how a disease is transmitted, and (2) the network's structure does not only help to understand the underlying context of the disease's spread, but it has an important role in finding efficient intervention and awareness plans.[36]

SNA in contrast to traditional statistical methods of analysis can combine the network structure with the distribution of the individual attributes (i.e., age, weight, ethnicity, etc.).[36] Furthermore, the network is time dependent since the interactions between vertices may change at each defined time unit.[3]

2.2.4   Study Design and Data Collection

Compared to traditional study designs in public health where data can be collected from each study participant before the entire study sample was recruited, for many network studies the whole network needs to be identified before data collection starts.[34] For example, to study the friendship relations between students in a school classroom, all the students in that room would be identified before starting to collect network data.[34] After that, collected data is organized in an N-by-N square matrix, and each data entry represents a relationship between a pair of vertices [34] (e.g., friendship relation between two classmates or in this thesis a connection/relationship between MRSA case - roommate or MRSA case - attending physician).

Data collection in SNA can be complete or bounded if all network members were identified and boundaries are clear (e.g., analysis of a substance abuse referral network), or incomplete if there are not clearly defined boundaries for network identification (e.g., elite business leaders in a community).[34] There are two approaches to identify network boundaries: (1) the "realist" approach, as perceived by the vertices (e.g., individuals) themselves; it corresponds to the actual social group/organization boundaries and (2) the "nominalist" approach based on the researcher's own rules to identify network boundaries. [50, 51] As John Scott noted in his book, if the network's boundaries are inaccurately identified by a researcher, the social network studied will be an imperfect representation of the full network.[50]

When network analysis focuses on the relationships within a set of vertices, the network is known as *one-mode* network.[51, 52] Networks may involve more than one set of vertices, and the relationships of interest refer to the connection of vertices in one set to those in the other set (e.g., patients and the attending physicians in a hospital).[51, 52] This is the case of a *two-mode* network.

Data collection methods most used in network studies are: (a) interview (face-to-face or by telephone), (b) direct observations of interactions among vectors, (c)experimental designs (e.g., a set of individuals is chosen and their interactions are observed in an experimentally controlled situation), (d) ego-centered (e.g., consists of a focal person "ego" and a set of "alters" who have connections with the "ego", and the measurements of ego-alters ties and alter-alter ties), (e) snowball sampling (e.g., the initial network has a small number of individuals who are then asked about their connections who may be included into the network. These new members of the network are approached and asked to nominate other potential network members), (f) small world (e.g., using method for networks with high clustering coefficient, and most pairs of vertices connected by short paths), and (g) diary (e.g., asking an individual to keep a continuous record on the other people with whom he/she interacts).[34, 51]

 In a hospital setting, the contact between patients and HCWs can be studied by direct observation- but this type of data collection may be expensive, and the networks obtained lack generalizability.[53] Where available, the development of electronic medical record data represents a great opportunity of providing accurate information regarding the epidemiologic links among inpatients and HCWs.[53]

The social network of a hospital is smaller and structured differently compared to a social network of an urban community.[48] Moreover, in relation to the hospital's structure, the contact patterns in the hospital are controlled by a hierarchy defined by departments, wards and rooms.[48] Also, the hospital's network includes patients, HCWs and visitors. The HCWs can be subdivided into different groups, such as nurses, technicians, housekeeping staff and medical doctors (e.g., residents physicians may visit more wards than nurses do and may carry pathogens from one ward to another).[48]

2.2.5.   Data Analysis

As previously mentioned, there are three broad methods for network analysis: (a) network visualization - graphical representation of the studied networks; (b) descriptive analysis of network properties - providing important information on the position of vertices/subgroups in the network, and on the entire network structure, and (c) stochastic and longitudinal network methods - for building and testing inferential and longitudinal network models.[34]

In this thesis the first two network analysis methods will be used for data analysis.

2.2.5.1   Network visualization

With this method, network data is presented in a graphic format which facilitates its qualitative interpretation. In addition, graphical representation of the studied networks helps to better understand the data and communicate the results of the analysis.[34] The network software used (i.e., Pajek, UCINET) can display networks in different ways.[34] For example, one display is represented by the "ring network" in which the vertices are arranged in an oval making hard to determine which vertex is more/less connected to the others. In comparison, the "energy" algorithm is used to position more connected vertices toward the center of the network which makes it easier to see the network's structure reducing overlapping of the links and vertices.[34]

Figure 6. Ring network display
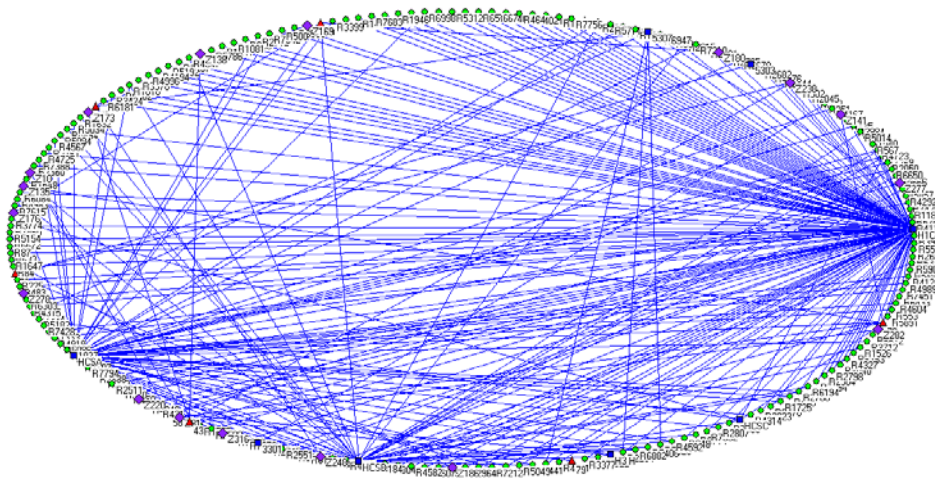
Ring network display- vertices are arranged in oval and it cannot distinguish which vertex is more/less connected to the other vertices.

Figure 7. Energy Kamada-Kawai displayed network
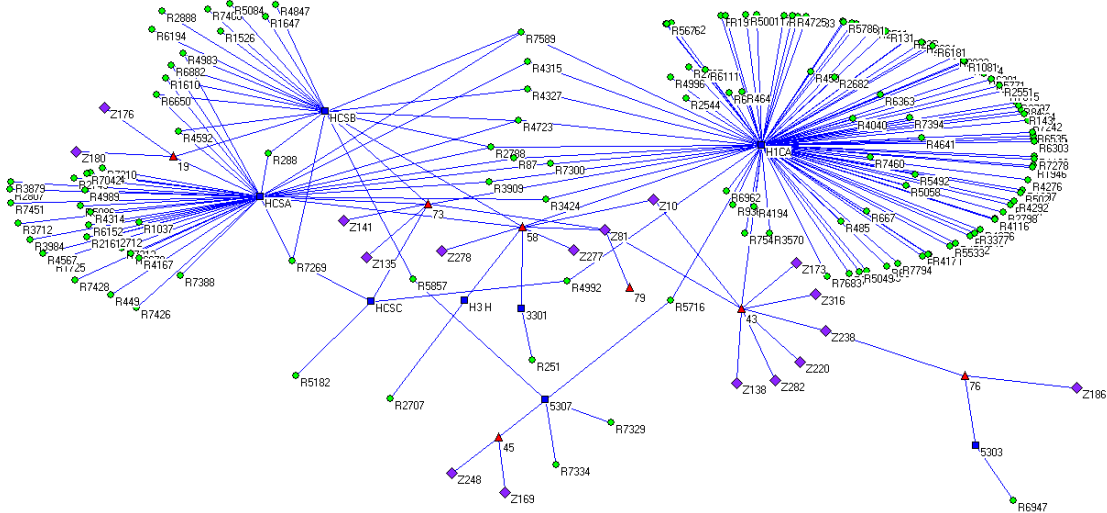
Using energy Kamada-Kawai to display the same network as in Figure 6

In this network display, the more connected vertices are positioned to the center of the network, and the overlapping of vertices and lines is reduced.

2.2.5.2   Descriptive Properties of Networks

<u>*Analysis at the individual level*</u> identifies the position of a vertex (a vertex can be identified as a person/group of people/place/organization/country, etc.) within a network.[34]

The most commonly used measure - *centrality measure* - indicates the status of a vertex within the network.[52] Each *centrality* measure reflects a different aspect of a vertex's network location.

In an undirected network (see Table 1 - Terminology and definitions in SNA) , a vertex's *degree centrality* represents the number of connections (or lines/ties) that a vertex has with other vertices.[54] Therefore, the *degree centrality* shows a vertex's level of network activity or involvement.[52] The degree *centrality* is the most commonly used measure of *centrality*.

The second measure of *centrality* is *betweenness centrality* which is defined as the frequency with which a vertex is found in an intermediary position along the geodesic paths (i.e., the shortest-length path) linking pairs of other vertices.[52] A vertex with high *betweenness centrality* can control relationships among other vertices.[52] Normally, this measure is used in networks having short paths between their vertices.

The third measure of *centrality* is *closeness centrality* and is represented by the sum of the geodesic distances from a given vertex to all others.[52]

The fourth *centrality* measure, *eigenvector centrality,* is sensitive to the presence and/or strength of connections, and the centrality of those vertices to which the focal vertex is linked.[52] In other words, the importance of an individual in a network depends on the importance of his/hers neighbors.[54]

As Borgatti noted in 2005, not all above mentioned *centrality* measures can be used when studying the spread of an infection. He argued that infection spreads by "reproducing rather than moving, it does not have targets (thus everybody can be infected), and does not take the shortest paths to the next vertex".[55] Therefore, when studying an infection transmission in a network, *degree centrality* and *eigenvector centrality* are the network measures to be used.[55] Borgatti interpreted these measures in his article (2005) as follows: *degree centrality* - a measure of immediate risk only (a measure of immediate influence - the ability to infect others directly or in one time period), and *eigenvector centrality* - a measure of long-term direct and indirect risk (based on this measure, a person's long-term risk of becoming infected is a function of the risk level of its contacts) .[55]

Valente et al (2008), in their study examining correlation between network centrality measures, concluded that there is a high correlation between *eigenvector centrality* and *degree centrality.*[56] Also, they suggested that vertices with high *degree centrality* are not necessary the most strategically located in the network, and on the other hand, those with high *eigenvector centrality* are linked to well-connected vertices, thus may influence many others in the network either directly or indirectly through their connections. [56]

Subgraph analysis: is used to identify and analyze subsets of vertices and their connections within the network.[34] This method is used to determine the cohesion of groups and characteristics of dyads, triads or other subsets.[34] This analysis can define locally dense regions within the network.[52] One common

measure used in this type of network analysis is *clique*.[52] *Clique* is defined as a maximal subset of vertices having density 1.0, which is equivalent to all my friends are friends with each other.[52] Another cohesion measure is the *k-connected component* (*k-core*) : a maximal subset of vertices reciprocally linked to one another by at least k vertex-independent paths.[52]

Network description on <u>the overall structure of the network</u> provides information on how connected a network is.[34] The most common measures used for this type of network analysis are: (a) network *order* defined as the number of vertices (N), (b) *size* representing the number of network ties/connections, and (c) the network *density* which is the *size* relative to the number of possible ties/connections.[52]

2.3 Description of The Ottawa Hospital

The Ottawa Hospital is a large multi-campus tertiary acute-care academic facility. In 2013-2014, there were 49,341 patient admissions on 1,127 beds.[57]

2.4 Hypothesis

We hypothesised that:

1) It is possible to build a social network of HCWs and places connected to patients colonized or infected with MRSA in a large tertiary acute-care hospital.

2) There is a difference between this healthcare network and a second built network including the HCWs, places and inpatients chosen as a control group in this study (see inclusion criteria).

3) After building the healthcare networks, and based on the analysis of the network structure and its characteristics, we can determine the role of healthcare workers and places in the transmission of MRSA infection in a large tertiary acute-care hospital.

To test this thesis's hypothesis, it was decided to define two reference periods for building the social networks. The two reference periods were outlined based on the hospital MRSA outbreak identification for each campus site, during the study period (see 3.3 Data Analysis). Note that the reference campus outbreak periods may not have been correlated to the actual outbreak periods at TOH which were declared using TOH Infection Prevention and Control case definitions and were defined by individual unit (and not by campus).

2.5 Ethics Approval

After the Thesis Proposal was approved, an electronic data request form (Data Specification Form) was submitted to the Performance Measurement Client Services at TOH, and in parallel an application for ethics approval was submitted to The Ottawa Hospital Science Network - Research Ethics Board (Protocol# 20140794-01H).

Since this study was conducted using electronic medical record data collected at TOH, no associated harms and risks were identified for the participants involved.

Every effort was made to ensure the privacy and confidentiality of patient data by de-identifying data sets, ensuring only those directly involved in the study had access to the study data, keeping data on password protected computers in locked offices and agreeing to destroy all associated study data by deleting files and erasing hard drives when the mandatory 15 years time frame has expired.

3.0   Chapter 3 - Study design and Methods

3.1   Study Design

This is a secondary data case-control study, using individual characteristics and network structure measures, conducted at The Ottawa Hospital (TOH) between April 1st, 2013 and March 31th, 2014. TOH is a 1,127 beds tertiary acute-care academic hospital, located on multiple campus sites. There were approximately 49,341 patient admissions during the study period.[57]

3.1.1   Study population

Adult patients (≥18 years of age) admitted to any acute-care campus of TOH (Civic, General and Heart Institute) between April 1st, 2013 and March 31st, 2014 were eligible for inclusion in the study. Eligible patients were identified, based on inclusion criteria, from TOH Infection Prevention and Control Program and TOH Data Warehouse (TOHDW). Patients have not been contacted directly to obtain any information. No identifying patient/HCW's personal information (e.g., medical record number, names, date of birth) have been used in this study.

3.1.2   Inclusion criteria

   a. **MRSA case group:**

   ➢   Adult patients 18 or over years old on the date of the hospital admission
       AND

   ➢   Adult patients admitted to TOH during the study period who underwent risk factor-based screening and were found to be MRSA positive (either colonized or infected). These patients were screened for MRSA based on certain *pre-defined risk factors*:

admission through the Emergency Department, all direct transfers (hospital, long-term or chronic care facility, rehabilitation center, seniors' residence, group home, prison, homeless shelter, transfer from one TOH campus to another TOH campus, including the University of Ottawa Heart Institute and the Rehabilitation Centre), and admission to an Intensive Care Unit, including transfers from another unit with TOH;

OR

➢ Adult patients admitted to TOH, during the study period, who were identified MRSA positive more than 48 hours after the hospital admission.

For the purpose of this study, cases' group included patients colonized with MRSA (uninfected), and as well as those with clinically evident MRSA infection. HA- and CA-MRSA cases were classified based on TOH case definitions (see both case definitions on Section 3.1.5 *Definitions*)

b. **Control group included:**

➢ Adult patients 18 or over years old on the date of the hospital admission

AND

➢ Adult patients admitted to TOH, during the study period, who underwent risk factor-based screening and were found MRSA negative

OR

➢ Adult patients admitted to TOH, during the study period, who shared a room with a patient who was diagnosed with MRSA during his/her hospital stay (i.e., shared period defined as the period of time between the patient admission date and the date of confirmed positive culture), and who were found MRSA negative on screening.

The MRSA negative patients included into the control group were similar to the patients included into the MRSA case group since they were matched by age, gender and campus. In addition, the controls had similar opportunities for MRSA exposure since most of them were chosen among the MRSA cases' roommates.

3.1.3   Exclusion criteria:

a. Adult patients who were admitted to TOH before April 1st, 2013, and after March 31st, 2014.

b. All adult patients admitted to TOH during the study period who did not undergo risk factor-based screening upon admission and did not share a room with a patient diagnosed with MRSA during his/her hospital stay.

c. MRSA case group - a patient identified as MRSA positive by Infection Prevention and Control Program was excluded from the group if the methodologist could not link the patient's medical record number and/or admission date to a valid inpatient encounter in TOHDW.

d. Control group - a patient initially identified as a control was excluded from the control group if he/she subsequently became a case at any point during the study period.

3.1.4   Definitions

As per Infection Prevention and Control Policies and Procedures at TOH:

MRSA colonized is a patient who is MRSA culture positive but who has no signs or symptoms of infection caused by the organism. The colonized patient can transmit the organism to the others.

MRSA Infected is a patient who is MRSA culture positive and who shows signs and/or symptoms of infection caused by the organism.

Screening: Microbiology swabs ordered or collected specifically to identify MRSA colonization.

Risk-based screening method was defined as the process of screening patients for MRSA based on certain pre-defined high-risk factors. These factors include: :

- admission through the Emergency Department

- all direct transfers (refer to _Direct transfer_ definition below)

- admission to an Intensive Care Unit, including transfers from another unit with TOH

- admission to The Rehabilitation Centre

Direct transfer: patients transferred from one of the following facilities: hospital, long-term or chronic care facility, rehabilitation center, seniors' residence, group home, prison, homeless shelter. Patients transferred from one TOH campus to another TOH campus, including the University of Ottawa Heart Institute and the Rehabilitation Center, are considered direct transfers.

New Nosocomial case of MRSA is identified in more than 48 hours after admission. If the previous hospitalization at TOH was within 2 months, consider _nosocomial_ unless the patient has stayed in another healthcare facility or other hospitalization in that 2 months period.

New Community case of MRSA is defined by the following: identified within first 48 hours of admission, unless it is clear that the organism was acquired nosocomially. If patient had prior hospitalization at TOH more than 2 months ago, consider as _community case_.

3.1.5   Outcomes

1) _The primary outcome_ was to determine the feasibility of building a social network of HCWs (e.g., attending physicians) and places (e.g., hospital rooms) connected to patients colonized or infected with MRSA in a large tertiary acute-care hospital. For each one of the three TOH campuses, the

calculated mean +2*standard deviation of the number of MRSA cases for 3 consecutive weeks since the start of the study period was used to determine the first day of an MRSA outbreak. Then two reference periods were established, one two-month period before the first day of the outbreak and the second two-month period after the first day of the outbreak. For each period, we built the corresponding social network for the MRSA case group and for the control group. Network visualization was used to build the healthcare networks using the social network program - Pajek [59]. The next step was to determine the network individual measures (i.e., degree centrality, eigenvector centrality), and overall network measures (i.e., size, density) for both groups by using descriptive properties of networks method. Finally, we compared the calculated median degree centrality measure using a non-parametric test (Wilcoxon–Mann–Whitney test) to find statistically significant differences between the two groups and reference periods. It is important to mention that the degree centrality measures calculated for all three TOH campuses did not have a normal distribution (i.e., left skewed), therefore to compare them a non-parametric test has been chosen. (Appendix D: Freeman Degree Centrality Histograms).

2) *The secondary outcome* was to show whether the network measures (e.g., degree centrality, eigenvector centrality) can be used to determine which vertex (MRSA patient, patient room, or attending physician) was most influential in the transmission of MRSA in the hospital's network. As well, the correlation between the two calculated centrality measures was used to see if it is possible to estimate the most influential network's individual/place in the MRSA transmission.

3.2 Methods

3.2.1 Data Collection

The data required for this study's analysis were obtained from TOH Infection Prevention and Control Program and TOH Data Warehouse.

TOH Infection Prevention and Control Program

TOH Infection Prevention and Control Program is an essential component of the quality patient care, aiming to reduce the risk of MRSA infection for patients, staff and visitors within TOH. TOH Infection Prevention and Control Program data was used to obtain a list of MRSA positive screened patients, and the MRSA positive patients (infected or colonized) identified by clinical specimens for the study period. As well, this data contained assessment of whether MRSA for each patient during the study period was hospital or community associated, based on criteria outlined previously.

The Ottawa Hospital Data Warehouse (TOHDW)

The majority of the patient data was collected from TOHDW. It contains integrated data from several source systems, and stores clinical, laboratory and administrative data that can be linked using common identification keys.[60] TOHDW has been backdated from 1996 and once weekly TOHDW administrators' abstract data from the many operational data systems of TOH.[60] The diagram of TOHDW is presented in Appendix B. TOHDW's datasets that were used to extract data to test the hypothesis in this study are presented in Table 2.

Table 2. The Ottawa Hospital Data Warehouse datasets and examples of variables included in these datasets

TOHDW Dataset	Sample of variables
Health Records Abstracts	Patient demographics, date/time admissions and discharge, entry and exit codes(entry e.g. clinic, emergency; exit e.g. discharged home, dead), name of the hospital the patient was transferred from
Encounter	Patient demographics(at the time of encounter), and unique identifiers, type of encounter, start/end date/time of the encounter, inpatient details (e.g. admission route, the nursing station (ward) for this inpatient encounter, patient room number, transferring hospital, diagnosis code), discharge disposition
Procedures	Date/time and duration of the procedure, ICD-10 code for the procedure (and procedure details), provider and anesthetist associated with the procedure
Service	Type of service (e.g., radiology, physiotherapy, lab), date/time when the service was ordered, performed and verified, date/time of service cancelation, name of the person who ordered, performed, verified and cancelled the service
Patient	Patient demographics
Laboratory Service	Laboratory results for each inpatient
Transfers	The patient service transferred to, number of days in service, code used to identify the provider being transferred to, date/time admitted to the service
Providers	Identifies the provider and service within the discharge record
Staffing Level	Uniquely identifies an employee Time Card, uniquely identifies an employee Time Card Entry, type of time card entry. Initial entry or adjustment entry (many adjustments),date the shift was worked or started if the shift crosses midnight, time the employee shift started, time the employee shift ended, number of hours worked, occupation code
Facilities	Facility code

After the MRSA cases were obtained from TOH Infection Prevention and Control Program, and were

linked to TOHDW Database to be validated (Figure 8), the following steps were taken to collect the data:

1) Identified age-group matched control group

2) Pulled data for Encounter characteristics (see Appendix C - Data Specification Form. Performance Measurement and Health Records, Dataset 1: Cohort Characteristics)

3) Created table for Patient-Room pairs using data from Inpatient Census History table

4) Retrieved data on Room/unit characteristics

5) Created table on Patient-Attending provider pairs using data from Inpatient Census History table

6) Created table for Unit-Nurse pairs

7) Create table for Patient-Roommate pairs

Figure 8. Flow diagram showing the process of linking MRSA cases to a valid Inpatient encounter in TOHDW based on Medical Record Number (MRN) and admission date

MRSA Cases from Infection Prevention and Control Program

April 1st, 2013 - March 31st, 2014

N = 749 unique MRNs

Exclusions

1. Missing admission date (N = 17)

2. Duplicates (N = 3)

3. Unable to link to TOHDW (N = 17)

MRNs linked to TOHDW

N = 712

Exclusions

1. No valid Inpatient encounter (some outpatient, medical day care, etc.) N = 49

2. Could not link Inpatient encounter based on admission date   N = 100

MRNs linked to valid Inpatient Encounter in TOHDW

N = 563

The steps taken to identify the matched control group were:

Step 1. Create the Control Group 1- which included all patients admitted at TOH, who screened negative and did not test positive at any point during the study period. (Figure 9)

Figure 9. Create Control Group 1 from TOHDW
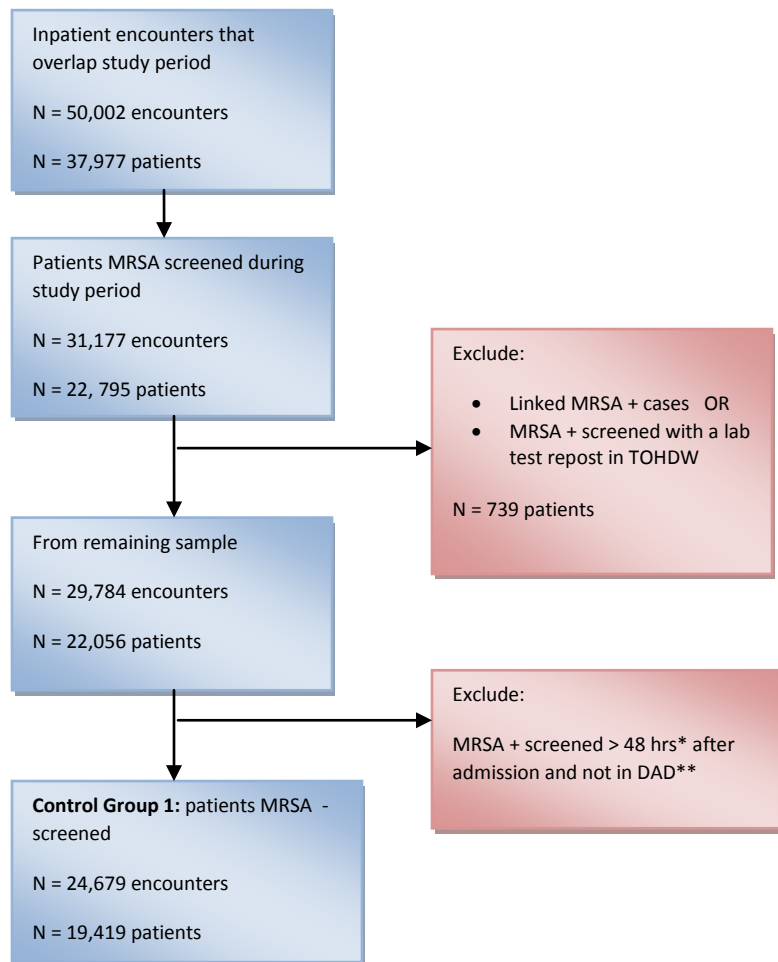
*To determine whether the MRSA testing was done over 48 hours after admission, it was calculated the difference between

admission date (encStartDtm) and lab specimen date (labSpecimenDtm).

** DAD: Discharge Abstract Database DAD (Inpatient hospitalizations)

Step 2. Identify the Roommate Control Group from Control Group. This group was represented by the

patients who shared room with a case during case's "exposure period" ("onset date" was considered the

date when the first MRSA positive lab test was confirmed; patient would be considered infectious before

and after that date. Therefore, the "exposure period" = onset date +/-10 days). (Figure 10)

Figure 10. Create Roommate Controls from Control Group 1


```
┌─────────────────────────────────┐
│ Control Group 1                 │
│                                 │
│ N = 24,679 encounters           │
│                                 │
│ N = 19,419 patients             │
└─────────────────────────────────┘
                 │
                 ▼
┌─────────────────────────────────┐
│ Patients who shared a room with │
│ a case at any point during      │
│ encounter                       │
│                                 │
│ N = 1,220 encounters            │
│                                 │
│ N = 1,241 patients              │
└─────────────────────────────────┘
                 │
                 ▼
┌─────────────────────────────────┐
│ Roommate Controls               │
│                                 │
│ Controls who shared a room with │
│ a case during "exposure period" │
│                                 │
│ N = 795 encounters              │
│                                 │
│ N = 795 patients                │
└─────────────────────────────────┘
```
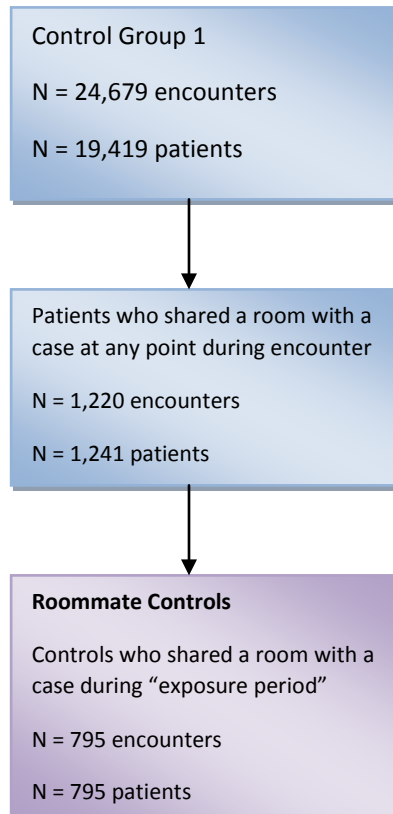
Step 3.   Matching Round 1: Roommate Controls to Cases (Figure 11)

In this first matching round the linked MRSA cases from TOH Infection Prevention and Control Program were matched with the controls who shared a room with a case during "exposure period" by age, campus and gender. The result was 529 MRSA case-control matched pairs.

Figure 11. Matching Round 1: Roommate Controls to Cases

Roommate Controls

N = 795 patients

Cases

N = 563 patients

1:1 Matching on

    a)   Age group (10-years)
    b)   Campus
    c)   Gender

N = 529 case control pairs
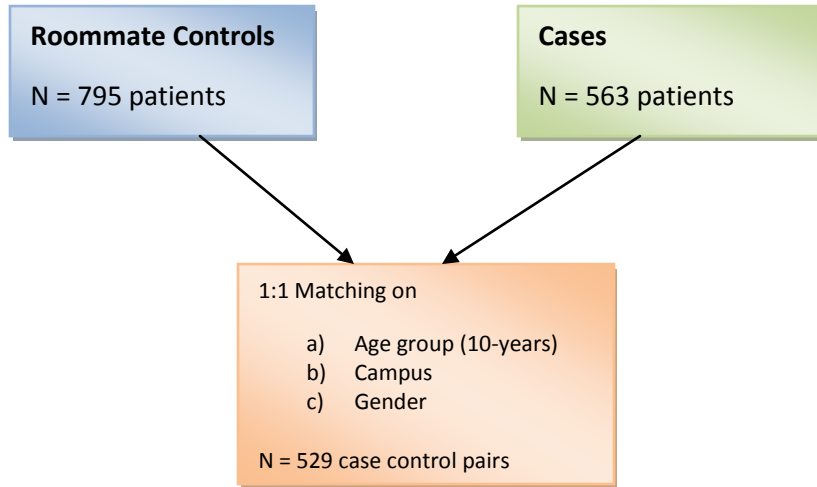
Step 4: Matching Round 2: Remaining Controls to Remaining Cases (Figure 12)

The remaining unmatched MRSA cases, after excluding the MRSA cases from the Rehab Centre not abstracted in DAD (thus, there would be incomplete patient information for data analysis) were matched in round 2 with the remaining MRSA negative patients based on same criteria as in round 1.

Figure 12. Matching Round 2: Remaining Controls to Remaining Cases

Remaining Controls

N = 18,890 patients

Remaining Cases

N = 34 patients

Excluded

Cases from Rehab Campus*

N = 16

1:1 Matching on

    a)   Age group (10-yr)
    b)   Campus
    c)   Gender
N = 18 case control pairs
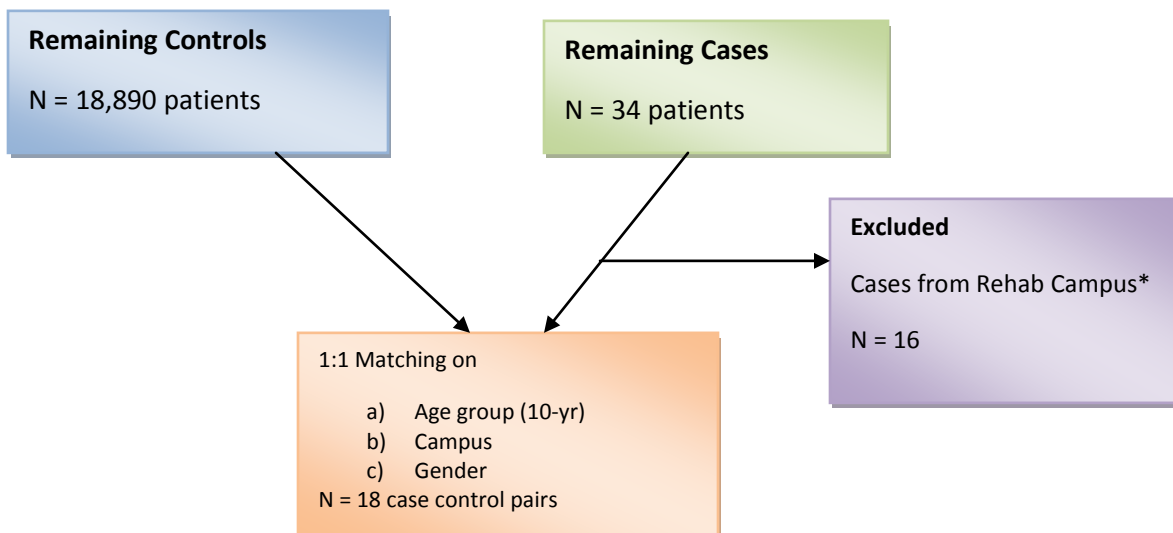
*MRSA cases from Rehabilitation Centre were not included in our study.

Step 5: Final Matched Cohort (Figure 13).

Figure 13. Final Matched Cohort

1:1 Matching on

    a)   Age group (10-yr)
    b)   Campus
    c)   Gender
N = 547 case control pairs

The cases and controls were matched 1:1 ratio by age, campus and gender. Each study group included

547 subjects.

The *data elements of interest extracted from TOHDW*:

Dataset 1(Cohort characteristics): patient ID (de-identified), encounter ID (de-identified), MRN (not

        provided to researcher, only used to link to Infection Control data) age, gender, postal code,

        encounter start/end, number of days in ICU, campus, Charlson Comorbidity score, died,

        discharge disposition, outcome status(cases/control), infection source (HA /CA-MRSA), test

        date

Dataset 2(patient-room pairs): encounter ID (de-identified), room, unit, primary activity of unit (i.e., ED,

        ICU), start date/time, end date/time.

It is important to mention that at TOH, patients are admitted to private rooms or rooms with more beds

(Intensive Care Unit, Acute Care Unit, Day Care Surgery Unit, etc). The way data were entered in

TOHDW for the studied period, it was not possible to link a patient with a specific place in these big units

(i.e., the number of the room a patient is in). Therefore, in the patient-room pairs' data collected for this

study, for many patient-room pairs the "room" actually was represented by a "unit" (e.g., J2IC - Intensive Care Unit, DCUS - Day Care Surgery Unit, etc). It was considered acceptable since in many cases in these big units a complete isolation of an infected patient is practically not feasible.

Dataset 3 (patient-attending provider pairs): encounter ID (de-identified), attending provider ID (de-identified), provider division, start date/time end date/time.

Dataset 4(patient-roommate pairs): encounter ID, room/unit, roommate ID (de-identified), start date/time, end date/time.

Dataset 5(unit-nurse pairs): nurse, unit, start date/time, end date/time.

The data collection from TOHDW was completed using statistical software (i.e., SAS®9.4 - SAS Institute Inc, Cary, NC, USA).

3.2.2   Quality Assurance measures

Periodic checks to ensure data accuracy were performed throughout the data collection process. Data obtained through TOHDW was cleaned by removing duplicate data, checking and correcting for missing values, and running frequency distributions and summary statistics using SAS®9.4 software program (SAS Institute Inc, Cary, NC, USA).

In addition, it was assumed that the data obtained from TOH Infection Prevention and Control Program Database was collected and entered in an appropriate manner.

3.3   Data analysis

After obtaining the datasets with the pairs of interest, two healthcare networks were built connecting cases (MRSA colonized and infected patients), respective controls with their roommate, rooms and attending physicians. Furthermore, based on the data obtained from the TOHDW, the cases, respective controls could not be connected with the attending nurses (nurses could be connected just with the units/wards in the hospital). In addition, the data related to other healthcare providers was inconsistent, therefore it was not able to link cases, respective controls with other healthcare professionals with whom the patients came in contact during their hospital stay.

To build the two healthcare networks, first the "excel" files containing the pairs of interest were converted to "net" files by using "CreatePajek" application.[59] Then using the "net" files, the two social networks were built for each hospital (Civic, General Campuses, and Heart Institute) using Pajek - (version 4.09, March 2016).[59] The steps followed to build the healthcare networks were:

a) Each MRSA case/control was paired with the room(s) they shared during their hospital stay at the same time. Then, the MRSA case/control was similarly paired with their roommates. After that, each case/control's roommate with whom each case/control shared the hospital room(s), was chronologically connected with the corresponding room(s). Finally, in the same chronological order each case/control was linked with the attending physician.

Since using the data for the entire period of study (one year) would produce very large social networks (which means that it would be hard to define network's boundaries, analyse and visualize it), it was decided to build smaller networks by defining their boundaries based on hospital outbreak identification.

b) Determined the mean+2*stdev (where stdev = standard deviation) of MRSA positive cases for every 3 consecutive weeks, for the entire period of study, and then compared these values with

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the number of positive MRSA cases identified each week for the same period. Furthermore, when the number of positive MRSA cases/week was found to be over the mean+2*stdev calculated for the previous three consecutive weeks, it was determined that the first day of that week represented the first day of a hospital MRSA outbreak. Moreover, considering first day of a MRSA outbreak as an index day, we defined a two-month pre-outbreak period (period 0 = period started two months before the index day and continued until the index day), and a two-month outbreak period (period 1 = period started on the index day and was terminated two months after the index day).

c) After defining the reference periods (period 0&1) for each studied hospital, the healthcare networks were built for MRSA cases, and controls chronologically linked with their hospital room(s), attending physician(s) and roommates using Pajek.

d) The healthcare networks were visualized and the measures of the overall structure of the network (i.e., the network size, density) were calculated using Pajek.

The descriptive properties of networks (i.e., degree centrality, eigenvector centrality) were calculated using UCINET for Windows - a software for Social Network Analysis (Borgatti, S.P., Everett, M.G. and Freeman, L.C. 2002, Harvard, MA: Analytic Technologies).[61]

Chi-square and t-tests were used for performing descriptive analysis of demographic data. A non-parametric test (Wilcoxon - Mann - Whitney test) was used to compare the measures of descriptive properties of networks between the two groups and two reference periods. This statistical analysis was completed with the help of SAS[®]9.4 software program (SAS Institute Inc, Cary, NC, USA).

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For creating a dynamic animation of one of the studied TOH campus's (i.e., Heart Institute) case-room-roommate-HCWs network during the two reference periods (period 0&1), it was used Pajek software program (version 2.05 - the only version compatible with Visone)[59], and Visone - 2.3.X (Java 6) - a software program for the analysis, visualization and animation of social networks.[62]

4.0 Chapter 4 - Results

4.1. Description of the Study Population

Between April 1st, 2013 and March 31st, 2014 The Ottawa Hospital (TOH) admitted 49,341 patients. During the same period of time, TOH Infection Prevention and Control Program confirmed 746 positive MRSA cases (colonizations and infections) at TOH. After the attempt to link the MRSA positive cases' data (using patient medical record number and admission date) obtained from TOH Infection Prevention and Control Program to a valid inpatient encounter in TOHDW, and two 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) (Table 3).

Approximately 40% of the 1,094 studied patients were 60 - 79 years old, 33% who were over 80 years old, 19% were 40-59 years old, and 8.4% were 18-39 years old. The patient median age for both groups was 72 years old. The median patient age at admission for CA-MRSA patients was 73 years old, and for HA-MRSA patients was 71 years old.

In both groups, 52% of the study participants were male. In the MRSA case group, there was no significant statistical difference in gender distribution between CA-MRSA and HA-MRSA infection type

The proportion of patients admitted from each campus for each group was as follows: 48% from Civic Campus, 38% from General Campus and 14% from the Heart Institute (Table 3).

There was no significant difference in the median length of patient hospital stay between the MRSA case group (11 days), and the control group (10 days) (p=0.66). The median number of ICU days spent by a

patient during hospital admission showed a significant difference between the MRSA case group (6 days) compared to the control group (14 days) (p=0.04).

Fifty-five (10.05%) of the 547 MRSA cases and thirty-eight (6.95%) of the 547 controls died during the studied period. There was no significant difference between the number of deaths in the two groups (p=0.06). There were 17 deaths (26%) among the 66 ICU MRSA cases and 6 deaths (20%) among the 30 ICU controls. Also, there was no significant difference between the number of ICU deaths among ICU MRSA cases and the number of ICU deaths among ICU controls (p=0.54), during the study period (Table 3).

The Charlson Comorbidity Index showed no significant difference between the two groups (p=0.79). The median value of the Charlson Comorbidity Index for both groups was equal to 2 (Table 3).

In relation to the identified MRSA infection type (see TOH case definitions - section 3.1.5), 58% of the MRSA cases were identified as community associated MRSA infection cases, and 41% MRSA cases were identified as nosocomial MRSA infection cases (1% cases were classified as "unknown" since no data were provided) (Table 3).

Table 3. Characteristics of the patients admitted to The Ottawa Hospital during the period of April 1st, 2013 - March 31st, 2014

Variable	VALUE	Cases	Controls	TOTAL	P-VALUE
		(N=547)	(N=547)	(N=1,094)	
Patient age at admission	Mean ± SD	68.64 ± 18.12	68.69 ± 18.10		0.96
	Median (IQR)	72.00 (57.00-83.00)	72.00 (58.00-83.00)		0.93
Charlson Comorbidity	Mean ± SD	2.17 ± 2.47	2.13 ± 2.52		0.79
	Median (IQR)	2.00 (0.00-3.00)	2.00 (0.00-3.00)		0.73
Number of deaths*		55 (10.05%)		547	0.06
			38 (6.95%)	547	
Number of ICU deaths*		17 (25.75%)		66	0.54
			6 (20%)	30	
Campus[1]	C	263 (48.1%)	263 (48.1%)	526	1
	G	209 (38.2%)	209 (38.2%)	418	
	HI	75 (13.7%)	75 (13.7%)	150	
Patient Gender	F	263 (48.1%)	263 (48.1%)	526	1
	M	284 (51.9%)	284 (51.9%)	568	
Number of ICU days	Mean ± SD	12.89 ± 24.03	16.20 ± 14.96		0.49
	Median (IQR)	6.00 (2.00-11.00)	14.00 (4.00-18.00)		0.04
Infection Type[2]					
	C	315 (57.6%)	0 (0.0%)	315	
	N	227 (41.5%)	0 (0.0%)	227	
	X	5 (0.9%)	0 (0.0%)	5	

| Length of hospital stay | Mean ± SD | 24.04 ± 40.13 | 18.77 ± 35.27 | 0.02 |
| | Median (IQR) | 11.00 (4.00-25.00) | 10.00 (5.00-21.00) | 0.66 |

* Deaths refer to all-cause mortality during the enrollment hospitalization.
[1]Campus: C - Civic, G- General, HI - Heart Institute
[2]Infection Type: C - Community Associated MRSA infection; N - Nosocomial or Hospital Associated MRSA infection; X - unknown infection type

4.2 Primary outcome: feasibility of building a healthcare network in a large tertiary care facility based on electronic medical record data

To define the reference periods (period 0=pre-outbreak period & period 1=outbreak period) for the network analysis, the index day was determined as the day when the MRSA hospital outbreak started. First, it was calculated the mean+2*stdev (where mean=moving average, and stdev=standard deviation) of MRSA positive cases identified for 3 consecutive weeks, and then compared these values with the number MRSA cases identified each week for the entire study period (Figure 12,13,14).

Figure 14. Civic Campus - comparing the number of MRSA positive cases identified in one week to the mean+2*stdev of the MRSA positive cases calculated for 3 consecutive weeks during the study period
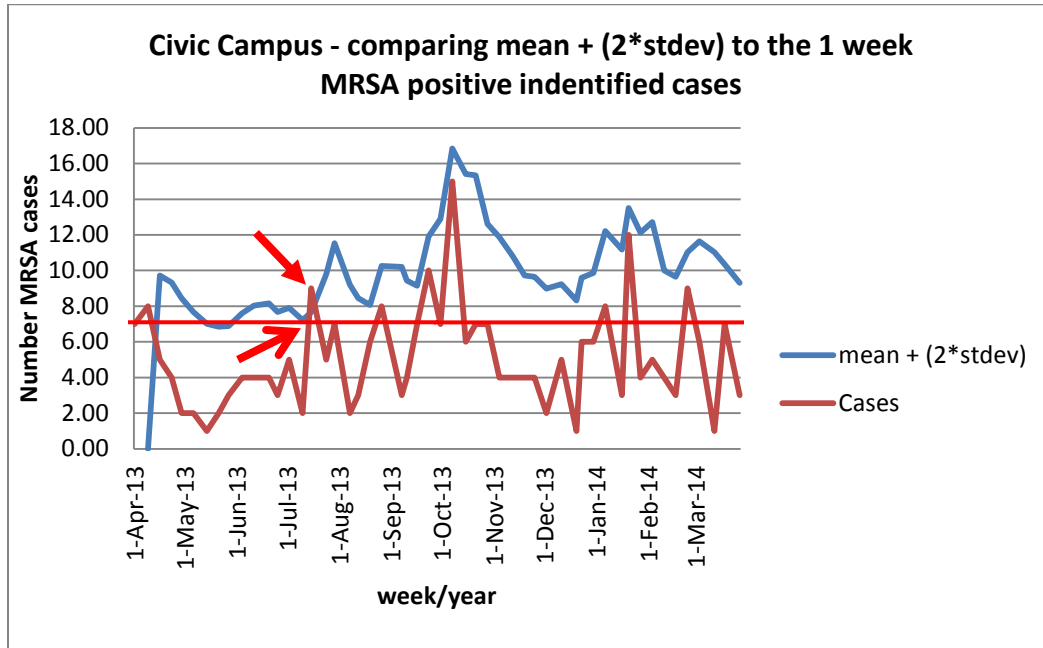
The red arrows in Figure 14 showed that at the Civic Campus, on the week starting on July 15, 2013, the number of MRSA positive cases identified (N=9) was over the value of mean+2*stdev (equal to 7.22) calculated for the previous three consecutive weeks. Therefore, the day of July 15, 2013 became the index day for Civic Campus.

Figure 15. General Campus - comparing the number of MRSA positive cases identified in one week to the mean+2*stdev of the MRSA positive cases calculated for 3 consecutive weeks during the study period
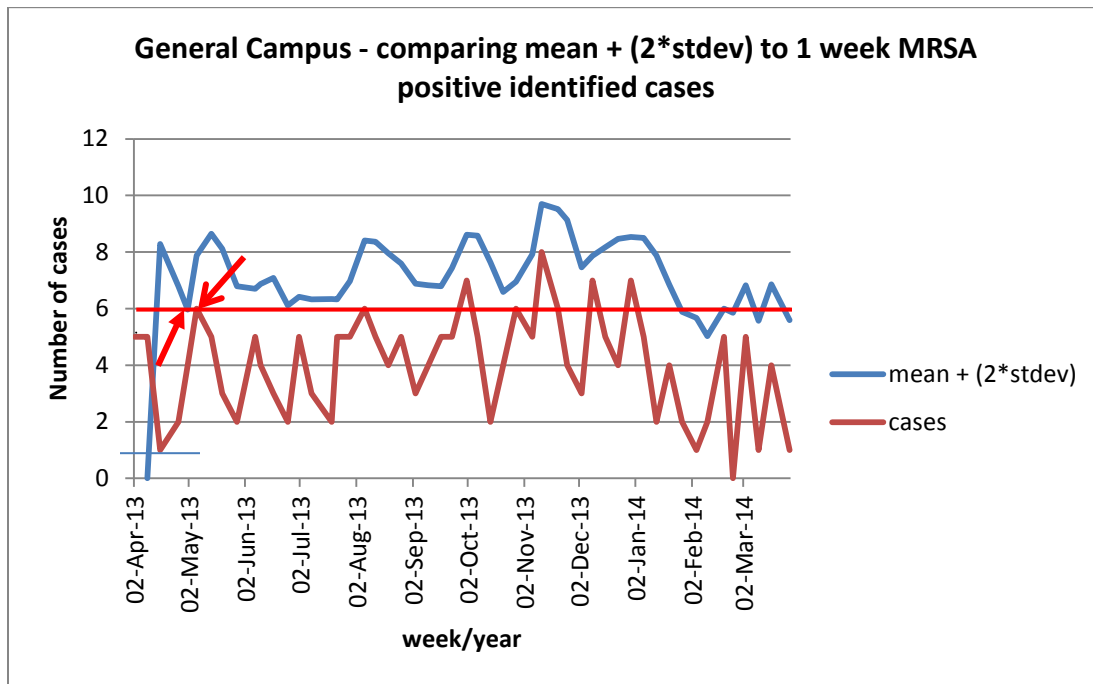
The red arrows in Figure 15 showed that at General Campus, on the week starting on May 6, 2013, the number of MRSA positive cases identified (N=6) was over the value of mean+2*stdev (equal to 5.96) calculated for the previous three consecutive weeks. Therefore, the day of May 6, 2013 became the index day for General Campus.

Figure 16. Heart Institute - comparing the number of MRSA positive cases identified in one week to the mean+2*stdev of the MRSA positive cases calculated for 3 consecutive weeks during the study period
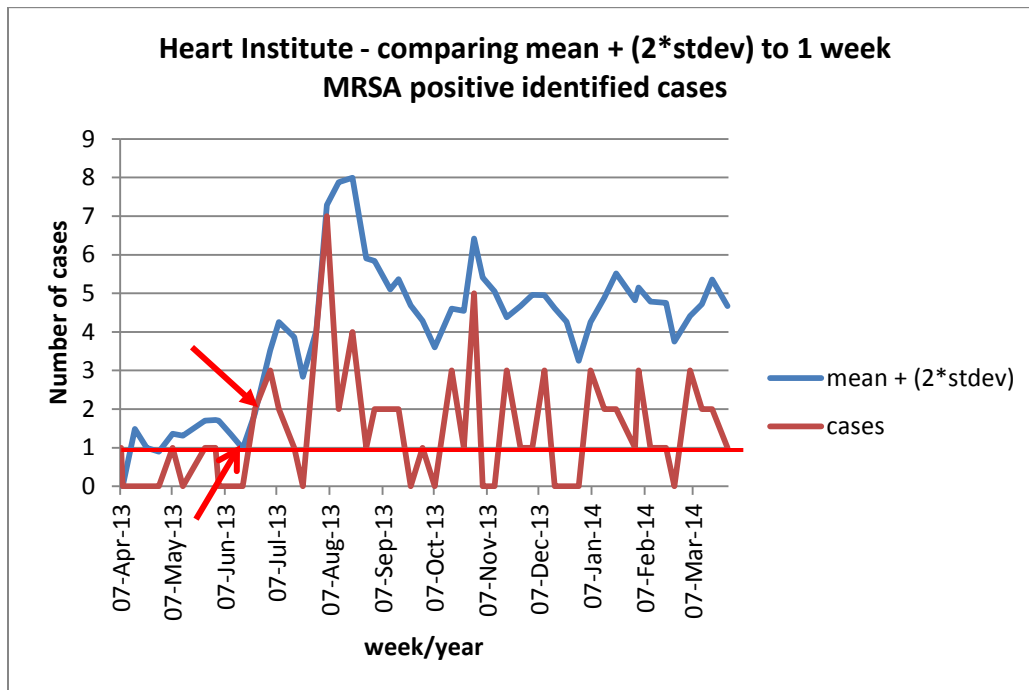
The red arrows in Figure 16 showed that at Heart Institute, on the week starting on June 24, 2013, the number of MRSA positive cases identified (N=2) was over the value of mean+2*stdev (equal to 0.98) calculated for the previous three consecutive weeks. Therefore, the day of June 24, 2013 became the index day for Heart Institute.

The index day and the period 0&1 were established for the 3 TOH campuses, and they are presented in the Table 4.

Table 4. Index day and reference periods (period 0&1) for TOH social network analysis

TOH Campus	Index day	Period 0	Period 1
Civic Campus	July 15, 2013	May 20 - July 14, 2013	July 15 - September 8, 2013
General Campus	May 6, 2013	March 11 - May 5, 2013	May 6 - June 30, 2013
Heart Institute	June 24, 2013	April 29 - June 23, 2013	June 24 - August 18, 2013

After defining the reference periods (period 0&1) for each hospital, we included in excel tables, in chronological order, the paired data on MRSA case/control - room, MRSA case/control - roommate, roommate of MRSA case/control - room, and MRSA case/control - attending physician. Then, the excel files were converted to net files (CreatePajek application) and used to build the networks (Pajek, version 4.09) (Figures 15, 16, 17).

The next step was to remove the Emergency room (ER) from the networks since ER is the first place in the hospital that most patients come in contact with when admitted, and did not provide valuable information for the analysis. After that, we rebuilt the networks.

Figure 17. Civic Campus - healthcare social networks for the period 0 (pre-outbreak) and period 1 (outbreak)

a. Civic Campus - MRSA cases-room-roommates-attending physicians network - period 0 (N=911)

Legend: ▲ **-** MRSA case; ■ - room; ● - roommate; ◆ - attending physician

b. Civic Campus - controls-room-roommates-attending physicians network - period 0 (N=409)

Civic Campus: comparison of the 2 groups' network graphs, for reference period 0, showed that the MRSA cases' network had a higher number of vertices and lines (also seen in Table 5). In addition, almost all vertices were connected in a big network component (there are just 2 components in this network, the second and smallest component included just 6 vertices). The most influential vertices in the network (with the highest number of connections) were rooms J2IC, F2IC (Intensive Care Unit) and E2NO (Neurologic Observation Unit) (see red arrows in graph17.a). On the other hand, the controls' network had a lower number of vertices and lines (also seen in Table 5), and the vertices were not as connected as in the cases' network (the network had 11 components). The most influential vertices in controls' network were rooms E2NO (Neurologic Observation) and F3PA (Post Anesthesia Care Unit) (see red arrows in graph 17.b).

c. Civic Campus - MRSA cases-room-roommates-attending physicians network - period 1 (N=1165)

d. Civic Campus - controls-room-roommates-attending physicians network - period 1(N=1646)

Legend: ▲ - control; ■ - room; ● - roommate; ◆ - attending physician

Civic Campus: During reference period 1, the number of vertices and lines increased in both networks (also seen in Table 5). The most influential vertices in MRSA cases' network were J2IC, F2IC (Intensive Care Unit), E2NO (Neurologic Observation), D2TR (Trauma Unit), and F3PA (Post Anesthesia Care Unit) (see red arrows in graph 17.c). Moreover, the most influential vertices in controls' network were the same rooms mentioned for the MRSA cases' network (see red arrows in graph 17.d). Each network had 5 components, a large component including majority of the network's vertices and four smaller components at the periphery of the network counting 3-20 vertices/each component. The number of patient rooms increased during this reference period in both networks.

Figure 18. General Campus - healthcare social networks for period 0 & period 1

a. General Campus - MRSA cases-room-roommates-attending physicians network - period 0

(N=210)

Legend: ▲ - MRSA case; ■ - room; ● - roommate; ◆ - attending physician

b. General Campus - controls-roommates-attending physicians network - period 0 (N=190)

Legend: ▲ - control; ■ - room; ● - roommate; ◆ - attending physician

General Campus: Both groups' network graphs for the reference period 0 showed comparable number of vertices and lines (also seen in Table 5). The most influential vertices in the MRSA cases' network were ICUN, ICUS (Intensive Care Unit) and 5AMA (Acute Monitoring Area) (see red arrows in graph 18.a). The most influential vertices in the controls' network were ICUN (Intensive Care Unit), DCUS (Day Care Surgery), and 5AMA (Acute Monitoring Area) (see red arrows on graph 18.b). For both groups, the majority of the network's vertices are connected in one big component (MRSA cases' network had another 8 small components and controls' network had another 2 small components).

c. General Campus - MRSA cases-roommates-attending physicians network - period 1 (N=338)

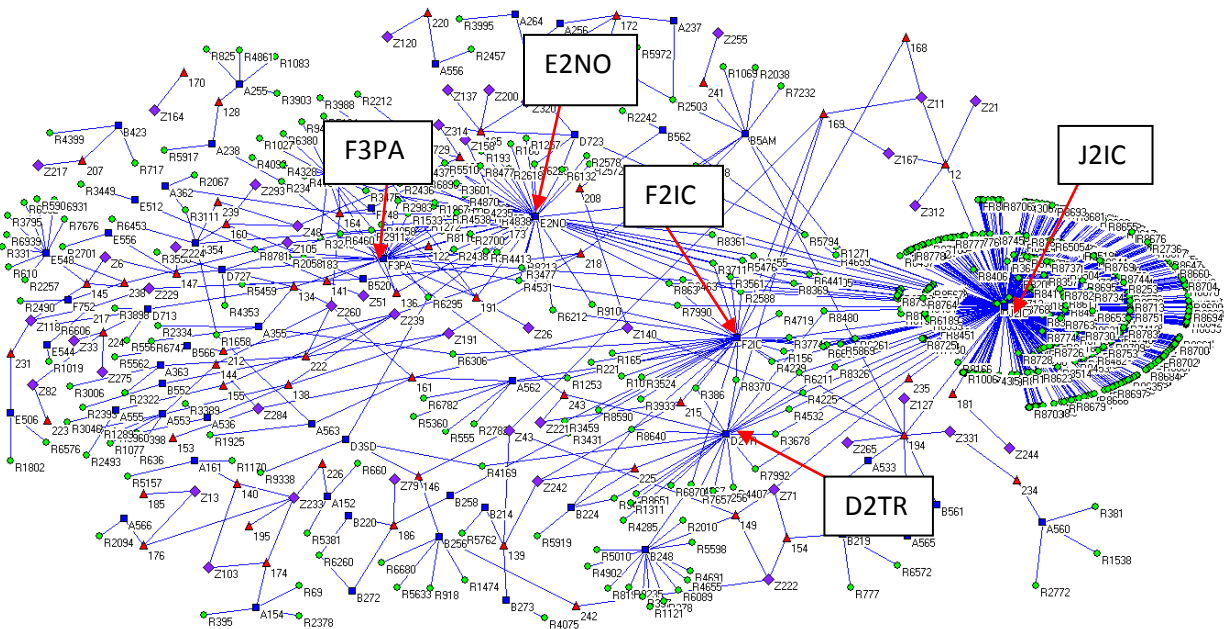Legend: ▲ - MRSA case; ■ - room; ● - roommate; ◆ - attending physician

d. General Campus - controls-roommates-attending physicians network - period 1 (N=406)
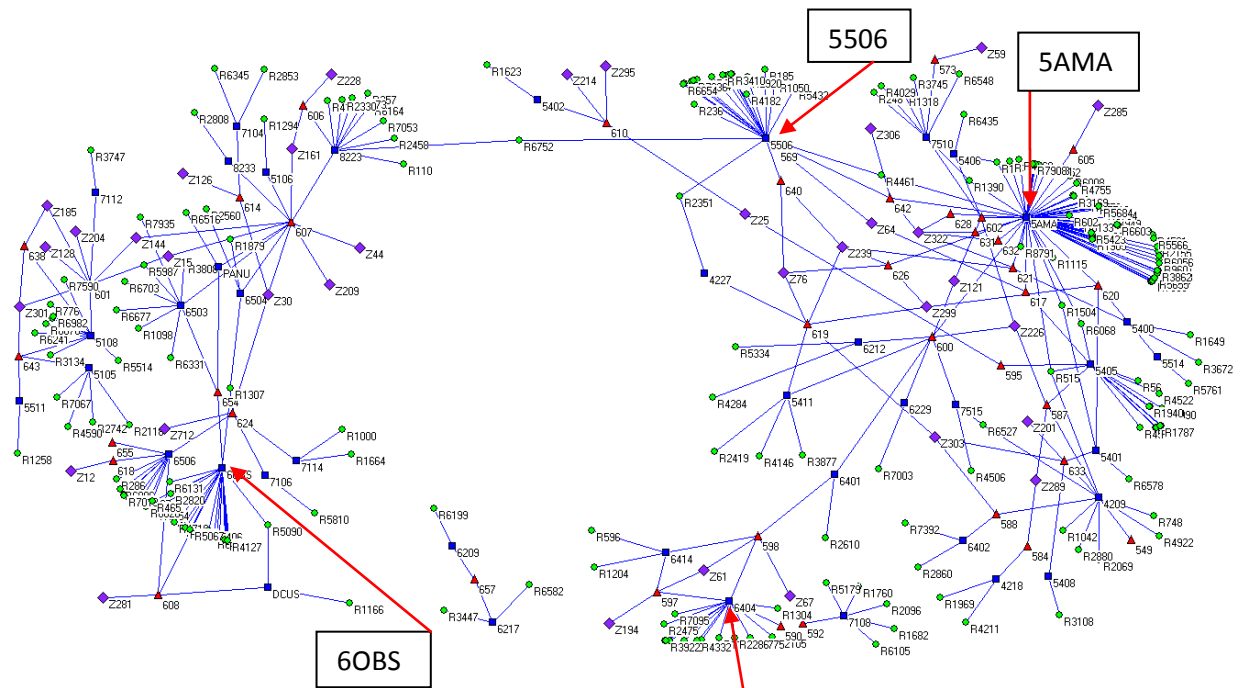
Legend: ▲ - control; ■ - room; ● - roommate; ◆ - attending physician

General Campus: During reference period 1, the number of vertices and lines increased in both networks compared to period 0 and are comparable (see also in Table 5). The most influential vertices in MRSA cases' network were ICUN, ICUS (Intensive Care Unit), and 5AMA (Acute Monitoring Area) (see red arrows in graph 18.c). Furthermore, the most influential vertices in controls' network were 5AMA (Acute Monitoring Area), 6404, 5506 (patient rooms in Short Rehabilitation Care Unit and Medical Day Care Unit), and 6OBS (6 Observation Unit) (see red arrows in graph 18.d). The majority of the vertices in both networks were connected in one big network component. Compared to period 0, the number of vertices connected in the big component increases (in period 1, the cases' network counted 7 other small components and the controls' network counted 2 other small components),The number of rooms increased during this reference period in both networks compared to period 0.

Figure 19. Heart Institute - healthcare social networks for period 0 & period 1

a. Heart Institute - MRSA cases-room-roommates-attending physicians network - period 0 (N=211)
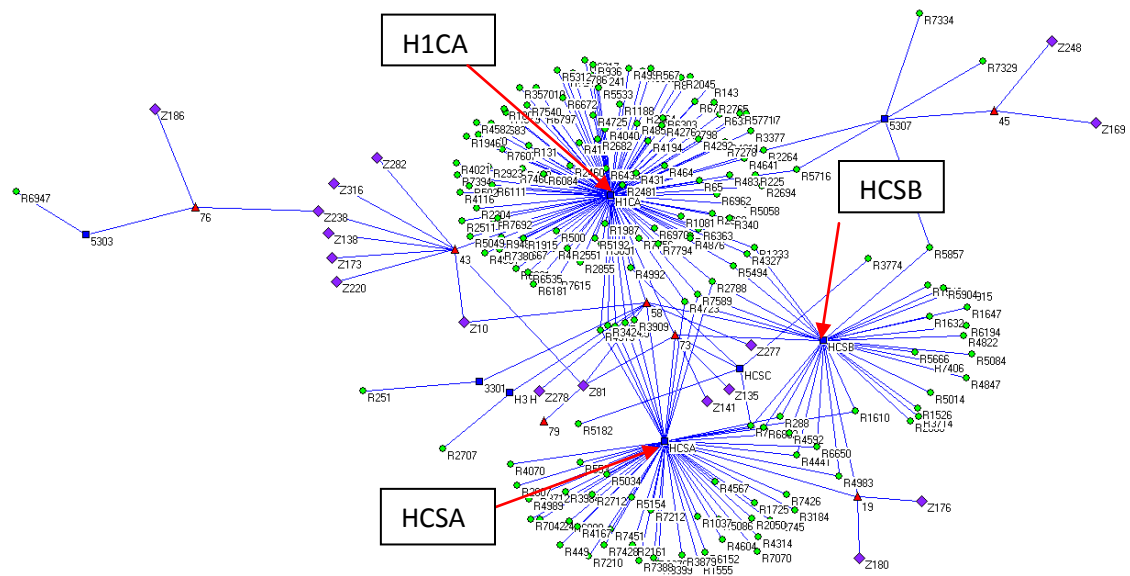
Legend: ▲ **-** MRSA case; ■ - room; ● - roommate; ◆ - attending physician

b. Heart Institute - controls-room-roommates-attending physicians network - period 0 (N=314)
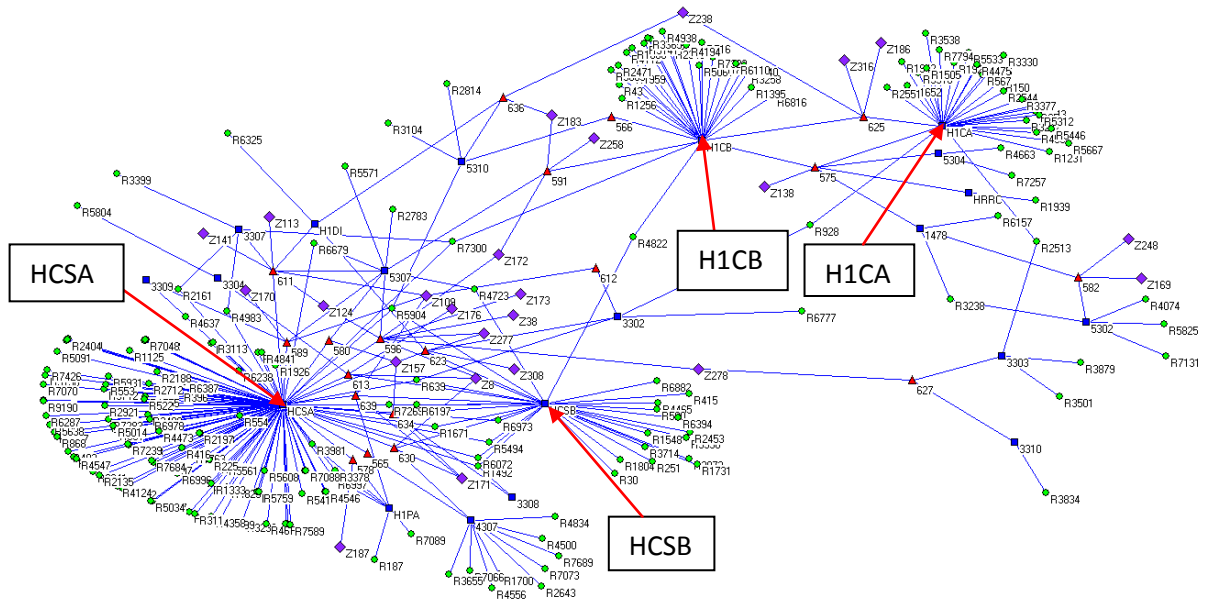
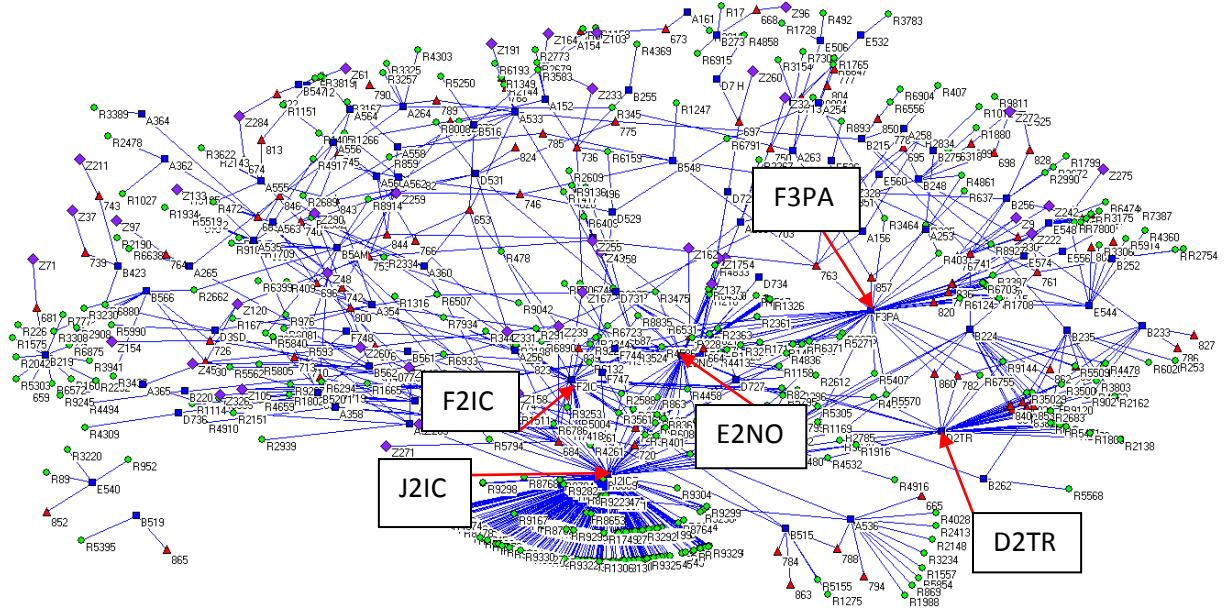**Legend:** ▲ - control; ■ - room; ● - roommate; ◆ - attending physician

Heart Institute: for the reference period 0, the MRSA cases' network had fewer vertices and lines compared to the controls' network (also see in Table 5). The most influential vertices in the MRSA cases' network were H1CA (or CCUA = Cardiac Care Unit A), HCSA and HCSB (or CSICUA and CSICUB = Cardiac Surgery Intensive Care Unit A and B) (see red arrows on graph 19.a). Also, the most influential vertices in the controls' network H1CA, H1CB (or CCUB = Cardiac Care Unit B), HCSA and HCSB (see red arrows on graph 19.b). All vertices are connected into one big network component in both networks.

c. Heart Institute - MRSA cases-room-roommates-attending physicians network - period 1 (N=335)
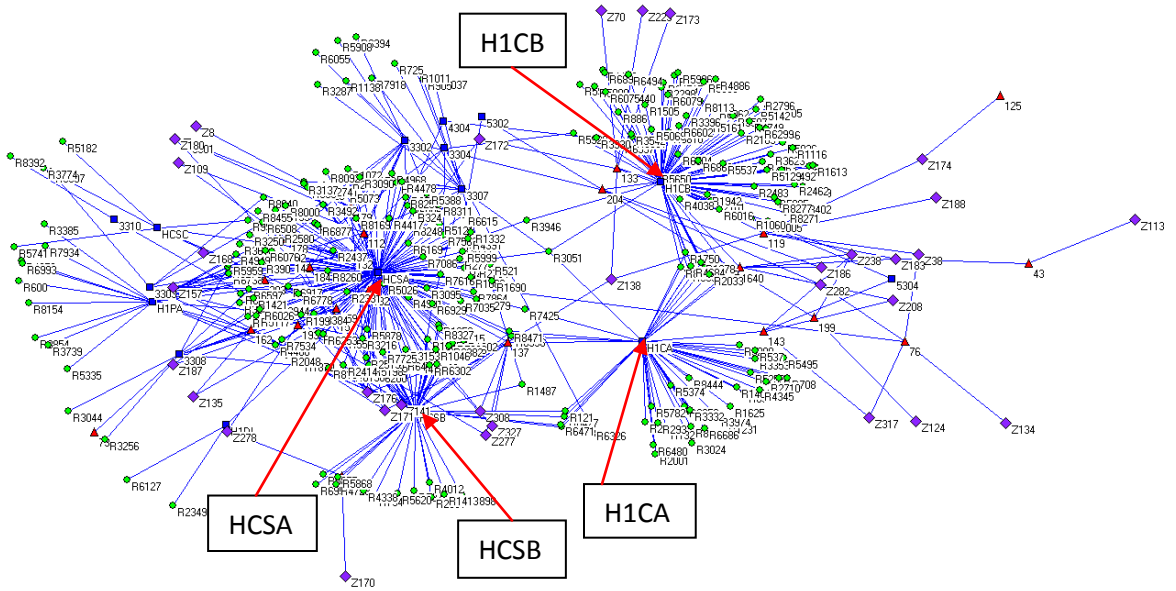
Legend: ▲ - MRSA case; ■ - room; ● - roommate; ◆ - attending physician

d. Heart Institute - controls-room-roommates-attending physicians network - period 1 (N=379)
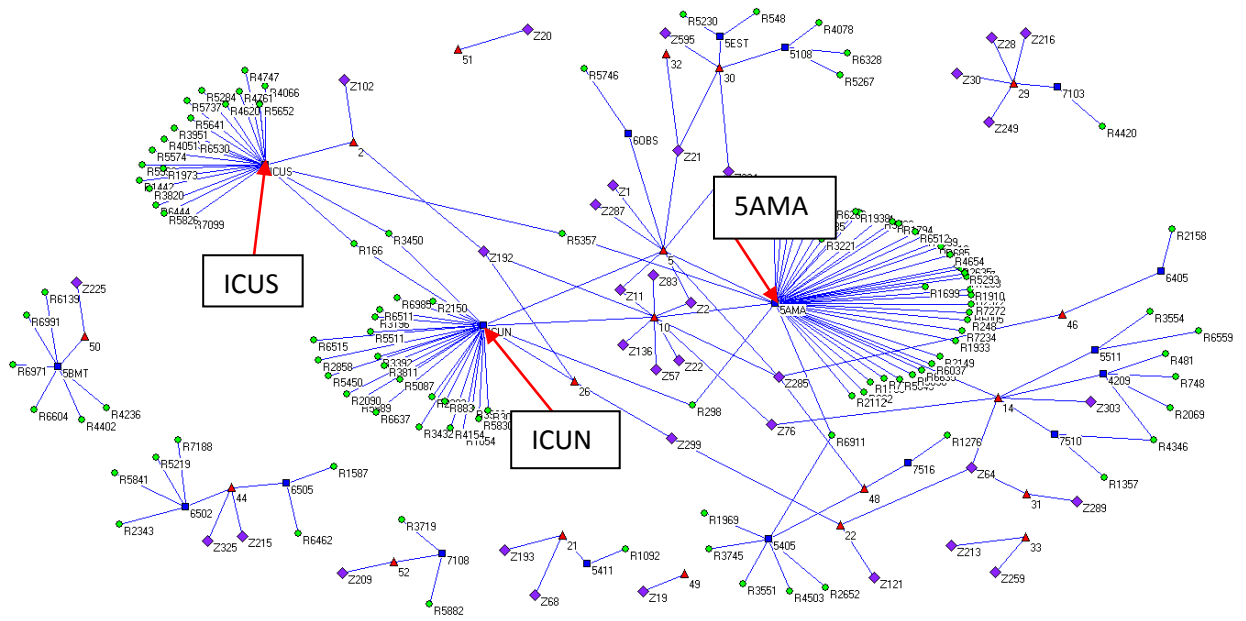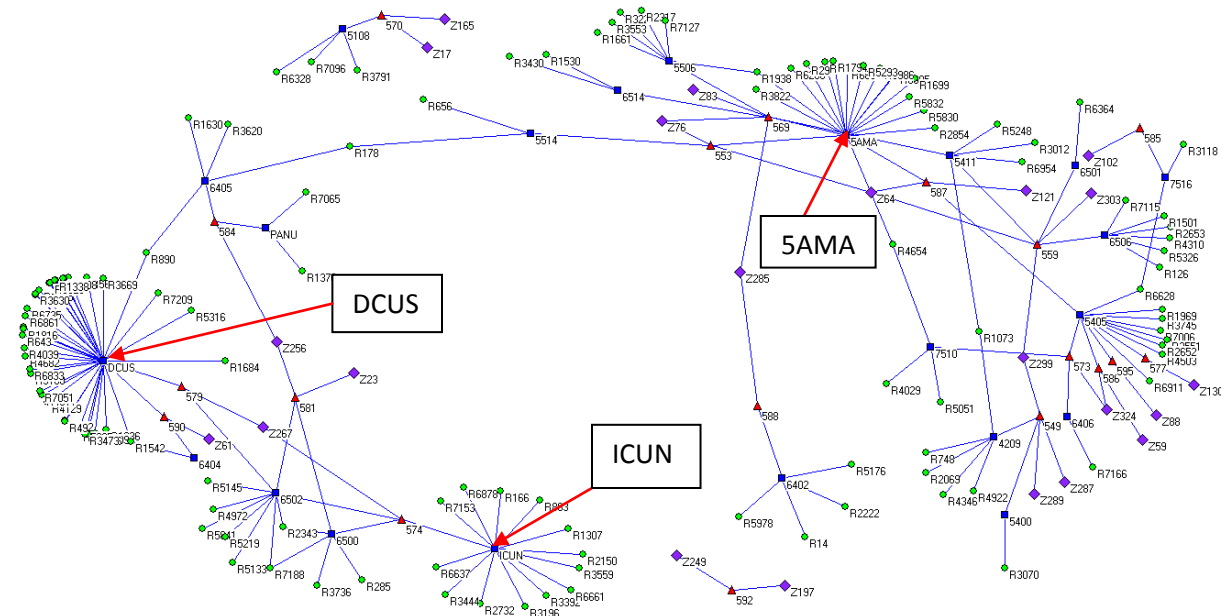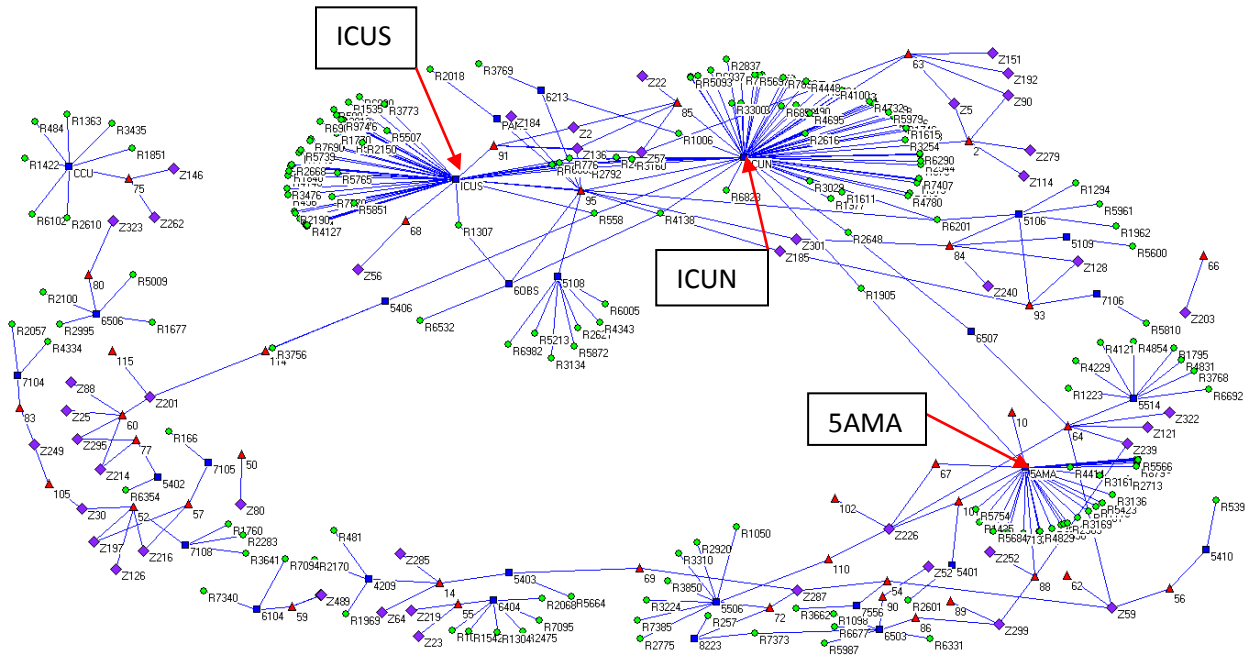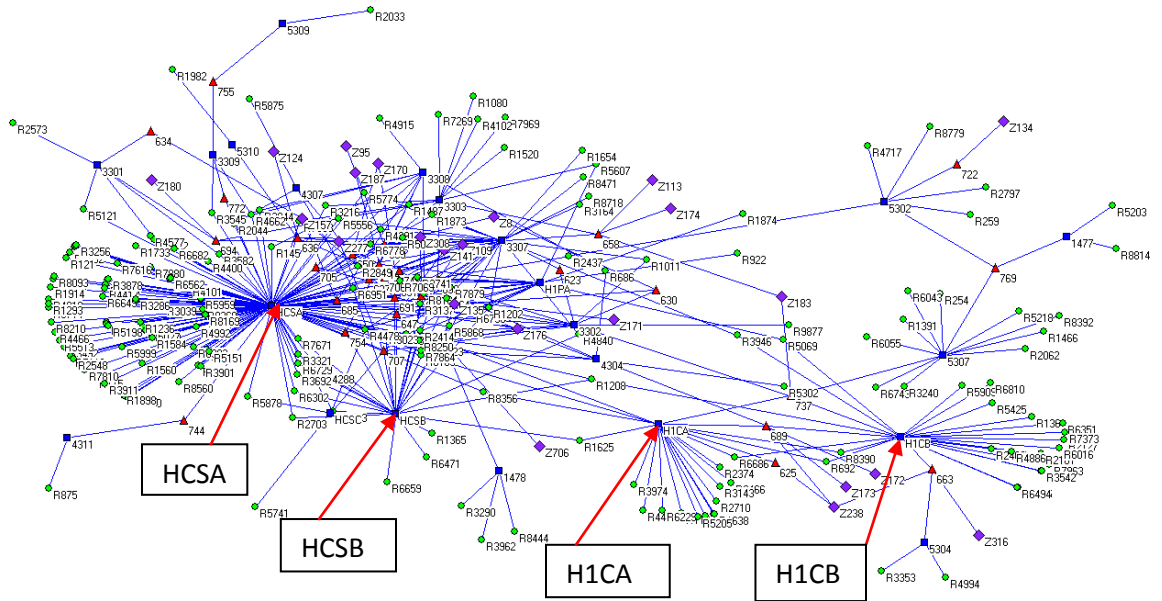

Legend: ▲ - control; ■ - room; ● - roommate; ◆ - attending physician

Heart Institute: During reference period 1, the number of vertices and lines increased but are similar when compared the groups' networks. The most influential vertices in MRSA cases' network were H1CA, H1CB (or CCUA, CCUB = Cardiac Care Unit A, Cardiac Care Unit B) , HCSA and HCSB (or CSICUA and CSICUB = Cardiac Surgery ICU A and B) (see red arrows in graph 19.c). As well, the most influential vertices in controls' network were the same rooms as those observed in MRSA cases' network, for this reference period (see red arrows in graph 19.d). All vertices were connected in one big network component in both networks. The number of rooms increased during this reference period, in both networks, compared to period 0.

After visualizing the networks, it was calculated the network's overall structure measures. It was found out that there are differences related to the number of vertices in the network, the number of network's connections (lines), and the network's density (Table 5).

Table 5. The overall structure network measures for both study groups and reference periods

	Period 0	Period 1
Civic Campus		
Cases		
Density	0.054	0.036
No. vertices	911	1165
No. lines	2856	4074
Controls		
Density	0.030	0.025
No. vertices	409	1646
No. lines	713	5165
General Campus		
Cases		
Density	0.049	0.038
No. vertices	210	338
No. lines	445	752
Controls		
Density	0.055	0.035
No. vertices	190	406
No. lines	353	893
Heart Institute		
Cases		
Density	0.130	0.107
No. vertices	211	335
No. lines	605	1500
Controls		
Density	0.084	0.095
No. vertices	314	379
No. lines	999	1538

As shown in Table 5, the number of vertices (including MRSA case/control, patient room, attending physician), and the number of lines (or ties) between the vertices increased during period 1 compared to period 0, for both groups and in all three TOH campuses' networks. On the other hand, there is a tendency of decreasing the network's density in period 1 compared to period 0 for both groups, in two of TOH

campuses' networks (Civic and General) and also in Heart Institute MRSA case group's network. The network's density calculated for the Heart Institute's control group network actually slightly increased in period 1compared to period 0.

Next, the network's individual measures (i.e., degree centrality) were calculated using UCINET. The estimated median degree centrality network measures between the two reference periods for each group and between the two groups for each period were compared. (Tables 6.a & 6.b)

Table 6.a. Comparing the Median Degree Centrality between reference periods for each study group and campus

	Period 0	Period 1	2-sided p value (Wilcoxon test)
Civic Campus			
Cases (N=36)			
Median Degree Centrality	5	19	0.001
Controls (N=45)			
Median Degree Centrality	5	20	<0.0001
General Campus			
Cases (N=19)			
Median Degree Centrality	6	11	0.03
Controls (N=18)			
Median Degree Centrality	8	18.5	0.001
Heart Institute			
Cases (N=7)			
Median Degree Centrality	29	60	0.20
Controls (N=19)			
Median Degree Centrality	28	32	0.29

Table 6.b. Comparing the Median Degree Centrality between study groups for each reference period and campus

Civic Campus			
Period 0			
	Case (N=36)	**Controls (N=36)**	**2-sided p value (Wilcoxon test)**
Median Degree Centrality	5	6	0.74
Period 1			
	Case (N=57)	**Controls (N=57)**	**2-sided p value (Wilcoxon test)**
Median Degree Centrality	**6**	**16**	**0.001**
General Campus			
Period 0			
	Case (N=18)	**Controls (N=18)**	**2-sided p value (Wilcoxon test)**
Median Degree Centrality	6.5	8	0.26
Period 1			
	Case (N=38)	**Controls (N=38)**	**2-sided p value (Wilcoxon test)**
Median Degree Centrality	**5**	**9**	**0.02**
Heart Institute			
Period 0			
	Case (N=7)	**Controls (N=7)**	**2-sided p value (Wilcoxon test)**
Median Degree Centrality	29	39	0.20
Period 1			
	Case (N=25)	**Controls (N=25)**	**2-sided p value (Wilcoxon test)**
Median Degree Centrality	29	28	0.86

As shown in Tables 6.a & 6.b, when we compared the median degree centrality (DC) values obtained for the two reference periods for MRSA cases, and respective controls, we found that:

- For the Civic and General campuses, there was a significant increase in median DC during period 1 compared to period 0, for both groups.
- For Heart Institute campus, there was no difference between the median degree centrality calculated for the two reference periods, and both groups.

Furthermore, when we compared the median DC between the two groups, for each reference period, the results showed:

- No difference between the median DC calculated for both groups and for all three campuses in period 0.
- In period 1: for the Civic and General campuses - the median DC of the control group was significantly increased compared to the median DC calculated for the MRSA case group. However, for the Heart Institute campus - no difference was found between the median DC calculated for both groups in period 1.

Finally, to better show the network's changes over time (i.e., over the two reference periods), time-series files of the network data were created with Pajek. These files were then used to produce a network dynamic animation with Visone (2.3.X version)

It is important to mention that the time unit in this dynamic animation is one day and each one of the 8 time series is equivalent to 2 weeks (there are 4 time frames for each reference period).

In this dynamic animation or "movie" we followed four MRSA cases in their hospital "journey" during the two reference periods.

We have chosen to follow MRSA case #19, case #43, case #58 and case #76 since these cases were admitted into the hospital during or before first reference period (pre-outbreak period), had a long length of hospital stay, therefore we could follow them during the two reference periods.

Case #43 was transferred to the Heart Institute from the General Campus one week before reference period 0. This patient had a length of hospital stay of 76 days, and was tested MRSA positive on May 4, 2013 (first week of reference period 0) with CA-MRSA. During the hospital stay, case# 43 was located in H1CA (or CCUA = Cardiac Care Unit A) for 52 days, then was moved to room# 5325 from where the patient was discharged home.

Case #58 was transferred to the Heart Institute from another acute-care hospital on the second week of the reference period 0. This patient had a length of hospital stay of 68 days, and was tested MRSA positive on May 14, 2013 (third week of reference period 0) with CA-MRSA. During the hospital stay, case# 58 was located in H1CA for 3 days, then was moved to rooms HCSA (for 1 day), HCSB (for 10 days), 3301 (for 13 days), H3 Hallway (for 8 minutes), 3327 (for 30 days), HCSB (for 3 days), and finally to room# 3322 (for 9 days) from where was discharged. The patient was tested MRSA positive when moved to unit HCSB. This unit later on had been connected to new MRSA positive identified cases. Moreover, at the time this patient was admitted to room H1CA the case# 43 was already in that room and tested MRSA positive. It is possible that case# 43 was the source infection for case# 58 since both were identified with CA-MRSA. It would have been helpful having the possibility to test if both patients were infected with the same MRSA type of strain.

Case# 19 was transferred to the Heart Institute from TOH - Ambulatory Care four weeks before reference period 0. The patient's length of hospital stay was 130 days, and was tested MRSA positive on April 7, 2013 (before reference period 0) with CA-MRSA. After hospital admission, case# 19 was located in

room# 3323 for 47 days (during this period of time was tested MRSA positive), and then was moved for 6 hours to HCSA, followed by 1 day in room# 1483. Finally, the patient was relocated to room# 3330 where stayed for the rest of the hospital stay (82 days) with a very short transfer of 2 hours to room HCSA (after 21 days of stay in room# 3330).

Case# 76 was transferred to the Heart Institute from another acute-care hospital on the fifth week of the reference period 0. Patient's length of hospital stay was 197 days, and was tested MRSA positive on June 7, 2013 (sixth week of reference period 0) with a CA-MRSA. After admission the patient was located in room#5325 for 14 days, then moved to room# 5303 for 5 days, and room# 5321 where patient stayed for 105 days.

The last two patients mentioned above had very long periods of hospital stay (over 100 days). Immediate after their hospital admission, these patients were isolated in small rooms, thus reducing the number of their connections with non-infected patients. However, these patients were moved to more than one room during their hospital stay.

It is interesting to mention that the rooms H1CA (Cardiac Care Unit A), HCSA and HCSB (Cardiac Surgery Intensive Care Unit A and B) were present in almost all time frames. In the first four time frames (period 0 = pre-outbreak period), these three rooms were connected with just few MRSA cases. As time is passing (see the last four time frames), the number of new MRSA cases connected with these rooms increased. This observation may be explained either by the fact that these rooms became actually a source of MRSA or the MRSA identified patients were isolated in allocated spaces in these rooms.

Figure 20. Time series of Heart Institute cases network data

Heart Institute - Time frame 1 (period 0, N=56)
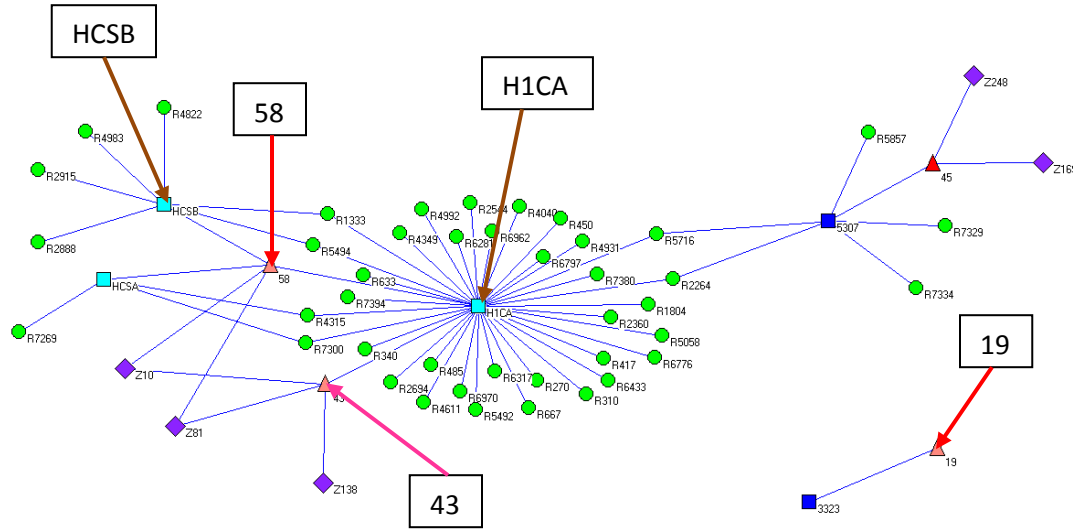
Legend: △ , ▲ - MRSA case; ◻ , ◼ - room; ● - roommate ; ◆ - attending physician

△ , ◻ - the MRSA cases and rooms that were followed on each time frame with explanations

Time frame 1 Legend:
- Red arrows indicate MRSA case #58 - connected to room H1CA (or CCUA = Cardiac Care Unit A) and room HCSB (or CSICUB = Cardiac Surgery Intensive Care Unit B), and MRSA case #19 - isolated in room # 3323
- Brown arrows indicate the room where the MRSA cases# 43 and 58 were admitted (H1CA) , and room HCSB where case#58 was then moved.
- Pink arrow indicates MRSA cases #43 - connected to room H1CA.
  During Time frame 1, MRSA case #43 was tested positive for MRSA.
- MRSA case #19 was already isolated to room #3323. This case was tested MRSA positive before Time frame 1.
- N =56 shows that there are 56 vertices in the network (patients, patient rooms and attending physicians)

Heart Institute - Time frame 2 (period 0, N=65)

Legend: △ , △ - MRSA case; ■, ■ - room; ● - roommate ; ◆ - attending physician

△ , ■ - the MRSA cases and rooms that were followed on each time frame with explanations

Time frame 2 Legend:
- Red arrows indicate MRSA case# 43 - connected to room H1CA, and MRSA case# 19 - connected first to room# 3323, then was moved to room HCSA (or CSICUA = Cardiac Surgery Intensive Care Unit A), room#1483, and room# 3330 during time frame 2.
- Brown arrows indicate rooms HICA, HCSA, HCSB connected to MRSA cases# 19, 43 and 58.
- Pink arrow indicates MRSA case# 58 connected to room HCSB. In this time frame case# 58 was tested positive for MRSA.
- There were 65 vertices in this network (N=65).

Heart Institute - Time frame 3 (period 0, N=107)

Legend: △ , ▲ - MRSA case; ☐, ■ - room; ● - roommate ; ◆ - attending physician

△ , ☐ - the MRSA cases and rooms that were followed on each time frame with explanations

Time frame 3 Legend:
- Red arrows indicate MRSA case# 19 - connected to room# 3330 first, then moved to rooms HCSA, HCSB and final patient return to room# 3330; MRSA case# 43 - connected to room H1CA, and MRSA case #58 - connected to room# 3301, then moved on H3 Hallway (for 9 minutes) and finally to room# 3327.
- Pink arrow points to MRSA case# 76 connected to room# 5325. The case# 76 was tested MRSA positive in this time frame.
- Brown arrows point to rooms H1CA, HCSA and HCSB connected to the MRSA cases# 19 and 43.
- There were 107 vertices in the network in this time frame (N=107).

Heart Institute - Time frame 4 (period 0, N=40)
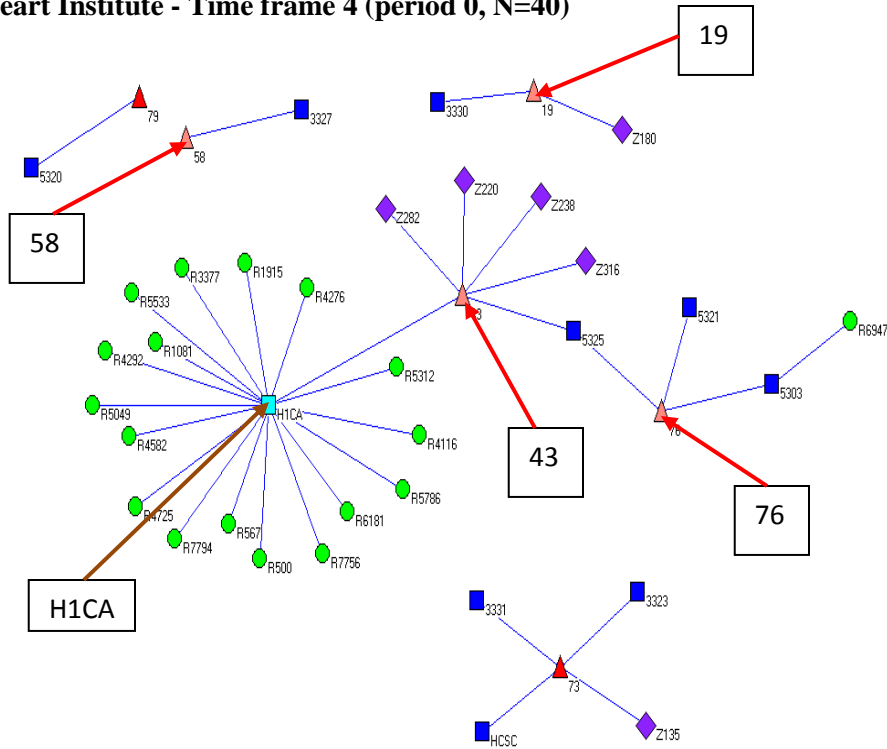
Legend: ▲ , ▲ - MRSA case; ■, ■ - room; ● - roommate ; ◆ - attending physician

▲ , ■ - the MRSA cases and rooms that were followed on each time frame with explanations

Time frame 4 Legend:
- Red arrows indicate MRSA cases #43 first connected to room H1CA, was then moved to room# 5325; MRSA case# 19 connected to room# 3330; MRSA case# 58 connected to room# 3327; and MRSA case# 76 first connected to room# 5325, was then moved to rooms# 5303 and 5321.
- Brown arrow indicates room H1CA connected to MRSA case#43.
- There were 40 vertices in this network (N=40) for this time frame.

Heart Institute - Time frame 5 (period 1, N=76)
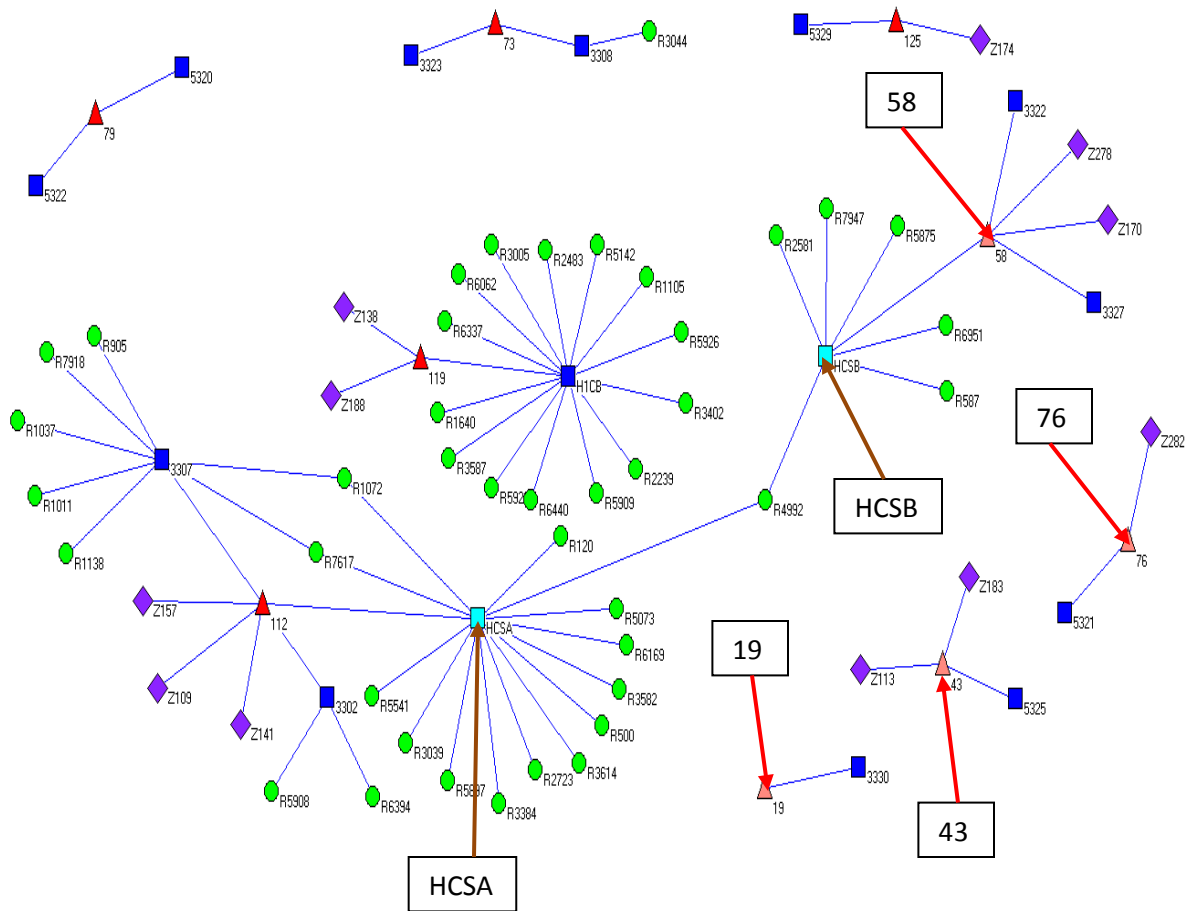
Legend: ▲ , ▲ - MRSA case; □, ■ - room; ● - roommate ; ◆ - attending physician

▲ , □ - the MRSA cases and rooms that were followed on each time frame with explanations

Time frame 5 Legend:
- Red arrows indicate MRSA case#43 connected to room #5325; MRSA case# 19 connected to room# 3330; MRSA case# 58 connected to room# 3327 then moved to room HCSB and 3322 ; MRSA case# 76 connected to room# 5321.
- Brown arrows indicate followed rooms HCSA and HCSB. There is a new case connected to room HCSA (MRSA case# 112)
- There were 76 vertices in this network (N=76).

Heart Institute - Time frame 6 (period 1, N=116)
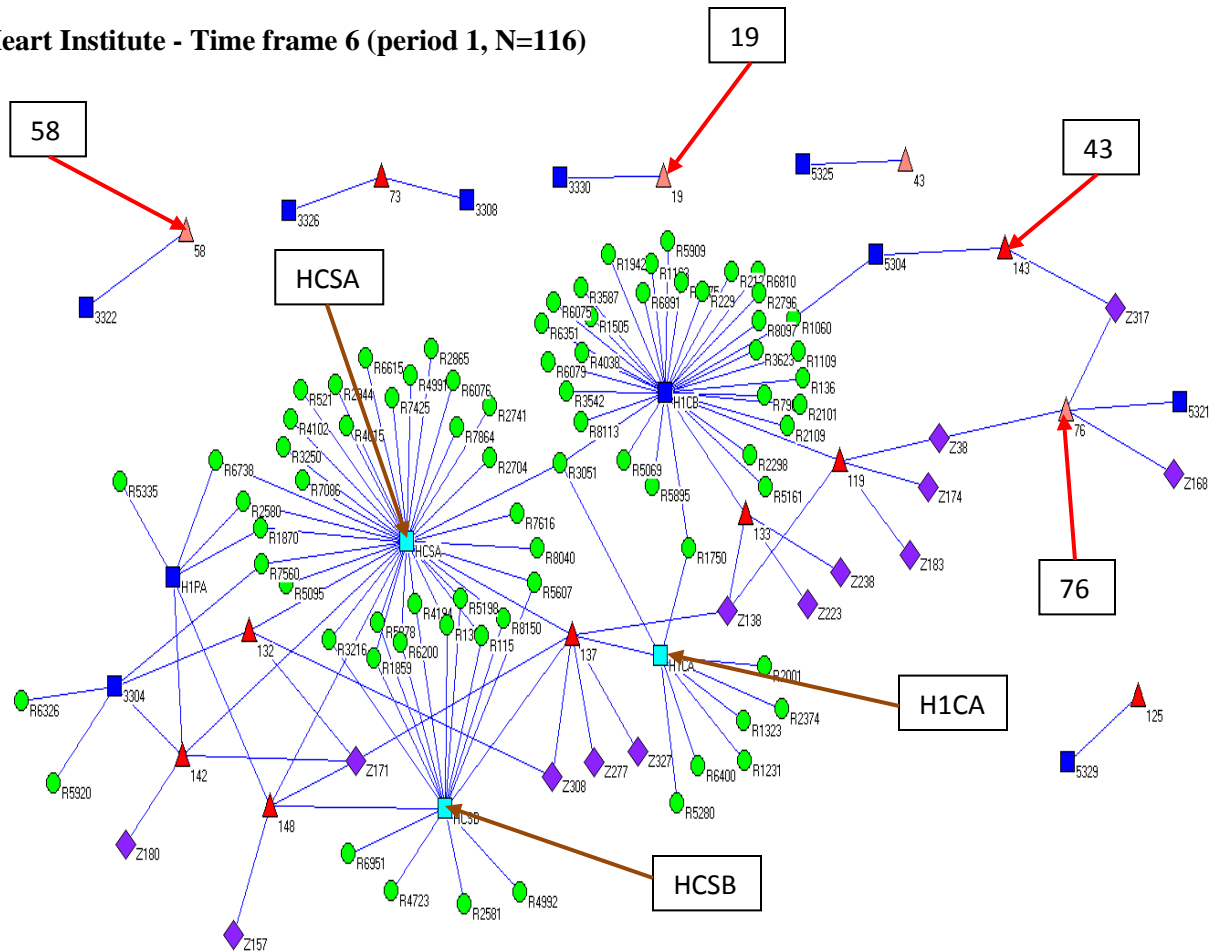
Legend: △ , ▲ - MRSA case; □ , ■ - room; ● - roommate ; ◆ - attending physician

△ , □ - the MRSA cases and rooms that were followed on each time frame with explanations

Time frame 6 Legend:
- Red arrows indicate MRSA cases#19 connected to room# 3330; MRSA case# 43 connected to room# 5325; MRSA case# 58 connected to room# 3322; MRSA case# 76 connected to room# 5321
- Brown arrows points to followed room H1CA, HCSA and HCSB which are now connected with new MRSA cases.
- There were 116 vertices in this network (N=116).

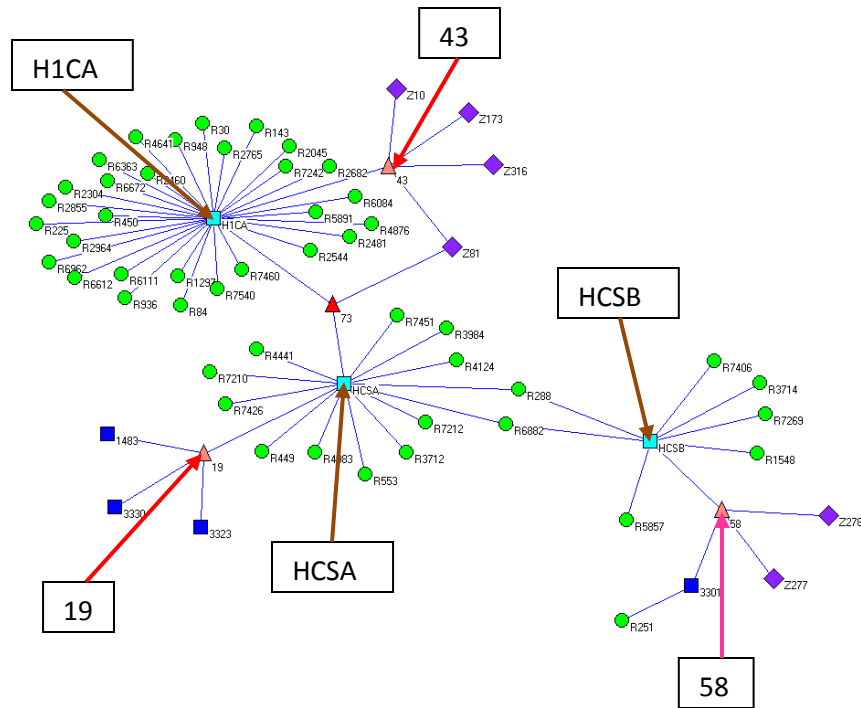**Heart Institute - Time frame 7 (period 1, N=151)**

Legend: △ , ▲ - MRSA case; □ , ■ - room; ● - roommate ; ◆ - attending physician

△ , □ - the MRSA cases and rooms that were followed on each time frame with explanations
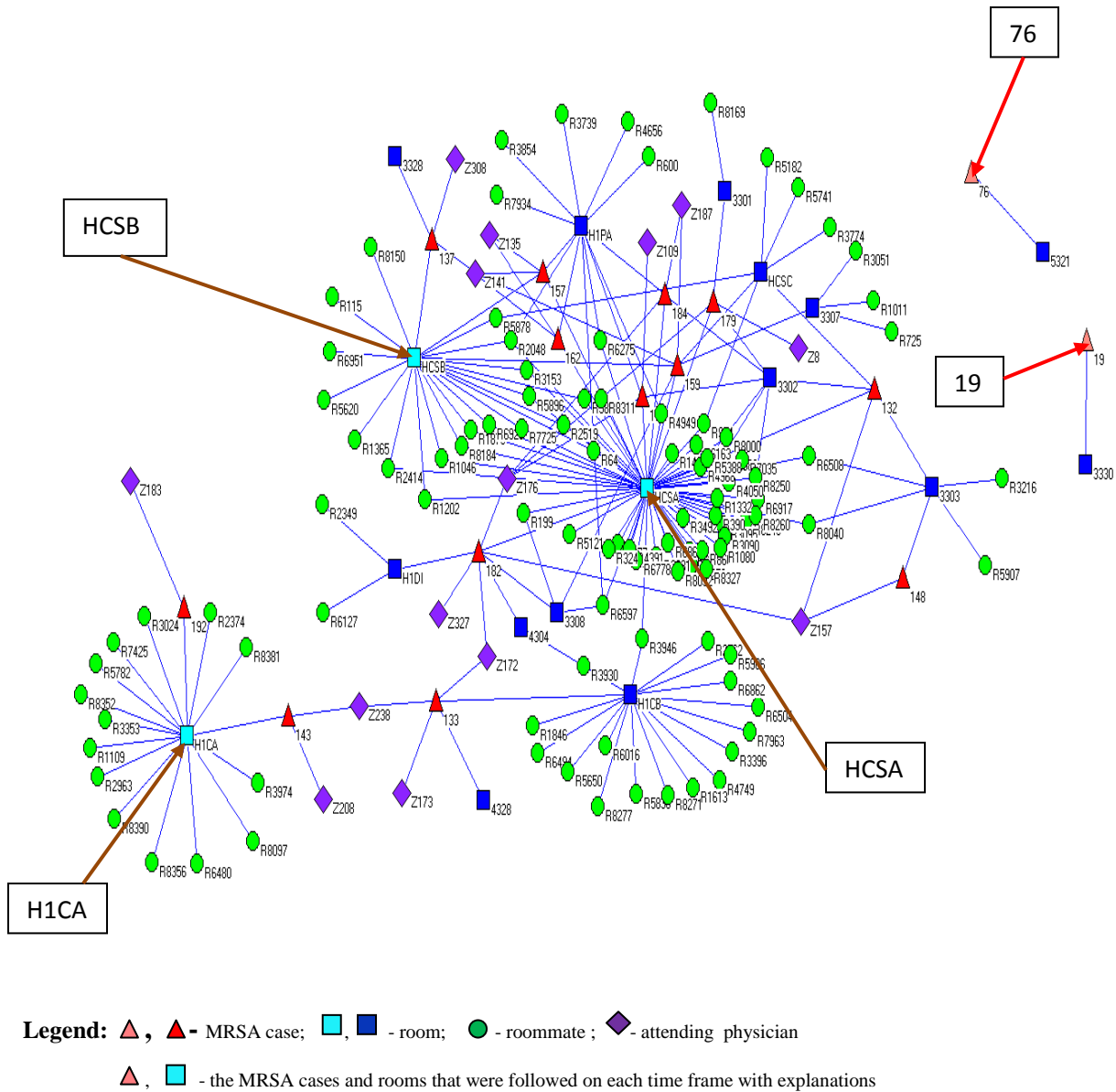
Time frame 7 Legend:
- Red arrows indicate MRSA cases #19 connected to room# 3330, and MRSA case# 76 connected to room#5321;
- Brown arrows point to followed rooms H1CA, HCSA and HCSB which in this time frame are connected with new MRSA cases (H1CA - cases# 143, 192; HCSA - cases# 132, 157, 159, 162, 178, 179, 184; HCSB - cases# 137, 157, 159).
- There were 151 vertices in this network (N=151).

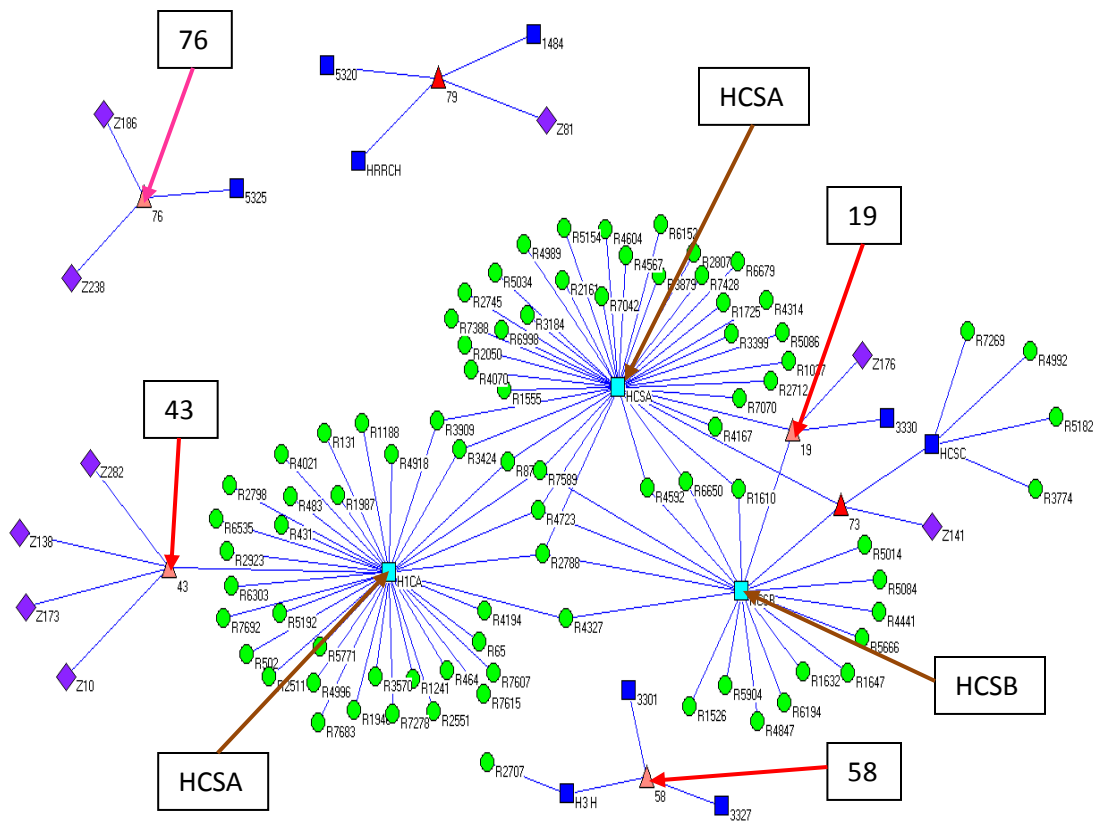**Heart Institute - Time frame 8 (period 1, N=117)**
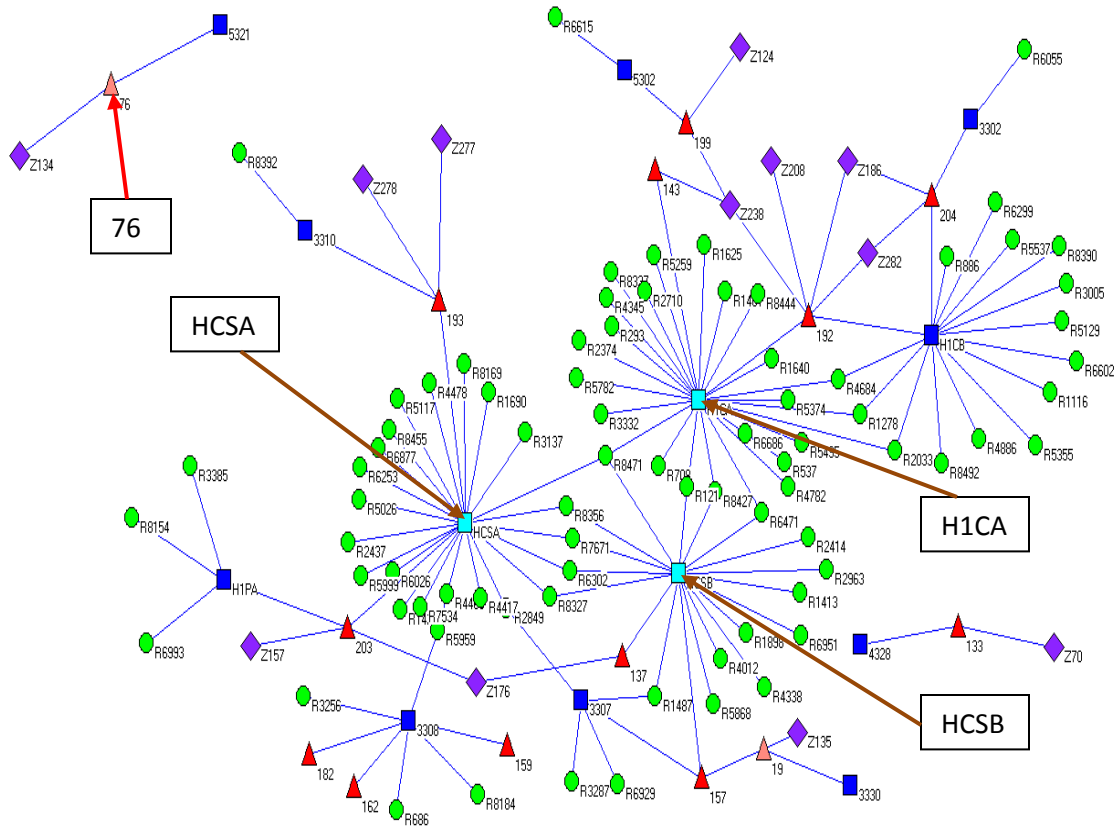
Legend: △ , ▲ - MRSA case; ☐, ◼ - room; ● - roommate ; ◆ - attending physician

△ , ☐ - the MRSA cases and rooms that were followed on each time frame with explanations

Time frame 8 Legend:
- Red arrows indicate MRSA cases# 76 connected to room # 5321;
- Brown arrow points to rooms H1CA, HCSA and HCSB which are now connected with same cases as in previous time frame or new MRSA cases (H1CA - cases# 143, 192; HCSA - cases# 193, 203, and HCSB - cases# 137, 157).
- There were 117 vertices in this network (N=117).

4.3   *Secondary outcome: identifying the most influential vertices in the hospital network contributing to the MRSA transmission*

Eigenvector centrality was the second centrality measure calculated for the MRSA case group, the hospital rooms and attending physicians connected to MRSA cases by using UCINET.

The calculated values of MRSA cases' degree centrality and eigenvector centrality were compared for each reference period and campus (Table 7-9).

Table 7. MRSA cases - UCINET results of highest Freeman degree centrality and eigenvector centrality for period 0&1 - Civic Campus

Civic Campus - Period 0

No.	Case ID number	Degree Centrality		No.	Case ID number	Eigenvector Centrality
1	12	771		1	12	0.699
2	108	188		2	117	0.081
3	117	125		3	92	0.060
4	92	105		4	108	0.001

Civic Campus - Period 1

No.	Case ID number	Degree Centrality		No.	Case ID number	Eigenvector Centrality
1	12	857		1	12	0.682
2	194	181		2	235	0.130
3	235	163		3	194	0.105
4	181	84		4	181	0.066

Table 8. MRSA cases - UCINET results of highest Freeman degree centrality and eigenvector centrality for period 0&1 - General Campus

General Campus - Period 0

No.	Case ID number	Degree Centrality		No.	Case ID number	Eigenvector Centrality
1	10	96		1	10	0.682
2	2	47		2	26	0.116
3	14	18		3	5	0.054
4	5	16		4	14	0.04
5	26	15		5	2	0.001

General Campus - Period 1

No.	Case ID number	Degree Centrality		No.	Case ID number	Eigenvector Centrality
1	95	72		1	85	0.463
2	85	63		2	91	0.323
3	91	57		3	95	0.314
4	2	26		4	2	0.172
5	63	23		5	63	0.141
6	68	11		6	68	0.06

Table 9. MRSA cases - UCINET results of highest Freeman degree centrality and eigenvector centrality for period 0&1 - Heart Institute

Heart Institute - Period 0

No.	Case ID number	Degree Centrality		No.	Case ID number	Eigenvector Centrality
1	43	153		1	43	0.699
2	73	91		2	58	0.047
3	58	33		3	73	0.047
4	19	29		4	19	0.004

Heart Institute - Period 1

No.	Case ID number	Degree Centrality		No.	Case ID number	Eigenvector Centrality
1	137	82		1	132	0.362
2	132	75		2	157	0.271
3	157	75		3	159	0.195
4	133	60		4	142	0.164
5	192	58		5	178	0.153
6	159	53		6	112	0.148
7	112	39		7	162	0.147
8	142	36		8	137	0.144
9	178	35		9	203	0.136
10	182	33		10	182	0.13
11	162	32		11	184	0.125
12	148	29		12	193	0.124
13	203	29		13	148	0.097
14	184	28		14	179	0.09
15	193	26		15	58	0.006
16	143	25		16	192	0.006
17	179	21		17	143	0.003
18	58	8		18	133	0.001

The calculated values of the degree centrality and eigenvector centrality, for the two reference periods, in Tables 7-9, showed MRSA cases with high degree centrality (DC) and eigenvector centrality (EC) (i.e., *Civic Campus* - **MRSA case #12** for both periods; *General Campus* - **MRSA case#10**, period 0& **MRSA case#85,** period 1; *Heart Institute* - **MRSA case#43**, period 0 & **MRSA case#132**, period 1). On the other hand, there were MRSA cases with high degree centrality but low eigenvector centrality value (i.e., *Civic Campus* - **MRSA case#108**, period 0& **MRSA case#194**, period 1; *General Campus* - **MRSA case#2**, period 0& **MRSA case#95**, period 1; *Heart Institute* - **MRSA case#73**, period 0& **MRSA case#137,** period 1).

Next, the MRSA cases' room degree centrality and eigenvector centrality calculated values for each reference period and studied campus were compared (Table 10-12)

Table 10. MRSA cases' Rooms - UCINET results of Freeman degree centrality and eigenvector centrality for period 0&1 - Civic Campus

Civic - period 0

No.	Room number	Degree Centrality		No.	Room number	Eigenvector Centrality
1	J2IC	1832		1	J2IC	0.707
2	E2NO	568		2	E2NO	0.004
3	F2IC	146		3	F2IC	0.003
4	F3PA	68		4	F3PA	0.000
5	B5AM	40		5	B5AM	0.000

Civic - period 1

No.	Room number	Degree Centrality		No.	Room number	Eigenvector Centrality
1	J2IC	2456		1	J2IC	0.707
2	E2N0	556		2	B5AM	0.003
3	D2TR	206		3	F2IC	0.001
4	F2IC	190		4	E2N0	0.000
5	F3PA	114		5	D2TR	0.000
6	B5AM	84		6	F3PA	0.000

Table 11. MRSA cases' Rooms - UCINET results of Freeman degree centrality and eigenvector centrality for period 0&1 - General Campus

General Campus - period 0

No.	Room number	Degree Centrality		No.	Room number	Eigenvector Centrality
1	ICUN	128		1	ICUN	0.566
2	5AMA	96		2	5AMA	0.422
3	ICUS	80		3	ICUS	0.002
4	5511	6		4	5511	0.002

General Campus - period 1

No.	Room number	Degree Centrality		No.	Room number	Eigenvector Centrality
1	ICUN	226		1	ICUN	0.561
2	ICUS	194		2	ICUS	0.427
3	5514	18		3	6OBS	0.031
4	5106	16		4	5108	0.031
5	5108	14		5	5106	0.001
6	6OBS	14		6	5514	0.000

Table 12. MRSA cases' Rooms - UCINET results of Freeman degree centrality and eigenvector centrality for period 0&1 - Heart Institute

Heart Institute - period 0

No.	Room number	Degree Centrality		No.	Room number	Eigenvector Centrality
1	H1CA	308		1	H1CA	0.706
2	HCSA	172		2	HCSA	0.042
3	HCSB	70		3	HCSB	0.010
4	HCSC	8		4	HCSC	0.001
5	3301	4		5	3301	0.001

Heart Institute - period 1

No.	Room number	Degree Centrality		No.	Room number	Eigenvector Centrality
1	HCSA	780		1	HCSA	0.695
2	H1CB	196		2	HCSB	0.123
3	HCSB	162		3	3307	0.023
4	H1CA	140		4	H1PA	0.023
5	H1PA	32		5	H1CA	0.021
6	3307	28		6	HCSC	0.019
7	HCSC	16		7	H1CB	0.002

Analyzing the data from Tables 10 - 12 for the two reference periods, it was observed that similar to the MRSA cases, there were rooms with high degree centrality (DC) and eigenvector centrality(EC) (i.e., *Civic Campus* - **Room # J2IC**, for both periods; *General Campus* - **Room# ICUN**, for both periods; *Heart Institute* - **Room# H1CA**, period 0& **Room# HCSA**, period 1). Also, there were rooms with high degree centrality but with very low eigenvector centrality value (i.e., *Civic Campus* - **Room# E2N0**, for both periods; *General Campus* - **Room# ICUS**, period 0& **Room#5514**, period 1; *Heart Institute* - **Room# HCSA**, period 0& **Room# H1CB**, period 1).

Finally, degree centrality and eigenvector centrality measures calculated for the attending physicians connected to MRSA cases, for each campus and reference period, were compared. (Table 13 - 15).

Table 13. Freeman Degree Centrality and Eigenvector Centrality measures calculated for Attending Physicians of MRSA cases - Civic Campus

Civic Campus - period 0

No.	Attending physician number	Degree Centrality		No.	Attending physician number	Eigenvector Centrality
1	**Z255**	7		1	**Z255**	0.000
2	**Z191**	5		2	**Z191**	0.000
3	**Z86**	4		3	**Z86**	0.000
4	**Z82**	4		4	**Z82**	0.000

Civic Campus - period 1

No.	Attending physician number	Degree Centrality		No.	Attending physician number	Eigenvector Centrality
1	**Z260**	6		1	**Z260**	0.000
2	**Z43**	5		2	**Z43**	0.000
3	**Z239**	5		3	**Z239**	0.000
4	**Z140**	5		4	**Z140**	0.000
5	**Z233**	5		5	**Z233**	0.000
6	**Z191**	3		6	**Z191**	0.000

Table 14. Freeman Degree Centrality and Eigenvector Centrality measures calculated for Attending Physicians of MRSA cases - General Campus

General Campus - period 0

No.	Attending physician number	Degree Centrality		No.	Attending physician number	Eigenvector Centrality
1	**Z285**	4		1	**Z2**	0.022
2	**Z2**	3		2	**Z11**	0.012
3	**Z11**	2		3	**Z285**	0.012
4	**Z76**	2		4	**Z76**	0.011

General Campus - period 1

No.	Attending physician number	Degree Centrality		No.	Attending physician number	Eigenvector Centrality
1	**Z226**	5		1	**Z57**	0.013
2	**Z57**	3		2	**Z226**	0.000
3	**Z287**	3		3	**Z287**	0.000
4	**Z239**	3		4	**Z239**	0.000
5	**Z201**	3		5	**Z201**	0.000

Table 15. Freeman Degree Centrality and Eigenvector Centrality measures calculated for Attending Physicians of MRSA cases - Heart Institute

Heart Institute - period 0

No.	Attending physician number	Degree Centrality		No.	Attending physician number	Eigenvector Centrality
1	**Z81**	5		1	**Z10**	0.015
2	**Z10**	4		2	**Z81**	0.011
3	**Z138**	2		3	**Z138**	0.010

Heart Institute - period 1

No.	Attending physician number	Degree Centrality		No.	Attending physician number	Eigenvector Centrality
1	Z157	6		1	Z157	0.008
2	Z176	6		2	Z135	0.007
3	Z141	5		3	Z141	0.007
4	Z109	4		4	Z176	0.006
5	Z135	4		5	Z308	0.006
6	Z187	4		6	Z109	0.005
7	Z308	4		7	Z187	0.005

As shown in Tables 13-15, the calculated eigenvector centrality values for all attending physicians who were connected to the MRSA cases during the reference periods were very low, practically closed to zero.

5.0   Chapter 5 - Discussion and Conclusions

5.1   Discussion

We have used electronic medical record data collected between April 1st, 2013 and March 31st, 2014 from TOH Infection Prevention and Control Program and TOH Data Warehouse to build two healthcare networks. The first network was built by connecting MRSA positive (colonized and infected) identified patients (the MRSA case group) with their roommates, hospital room(s) and the attending physician(s) for the two reference periods. The second network included MRSA negative screened patients at the hospital admission and MRSA negative tested patients during their hospital stay (control group) linked with their roommates, room(s), and attending physicians for the two reference periods. The MRSA cases and controls were matched 1:1 based on age, campus and gender.

Demographic results showed the median patient age at admission for both groups was 72 years old. The median patient age at admission for CA-MRSA cases was 73 years old and for HA-MRSA cases was 71 years old. Nichol et al (2013) in their study of changing MRSA epidemiology in Canada between 2007-2011, indicated that the median patient age for CA-MRSA (43 years) was significantly lower (p<0.0001) compared to the median patient age for HA-MRSA (68 years).[7] This significant difference in patient age compared to our study's results might be explained by our inclusion and collection data criteria (i.e., including in the study only adult 18 or over years old inpatients, and excluding those 202 cases whose records could not be linked to a valid inpatient encounter in TOHDW). In addition, our cases were classified as HA- or CA-MRSA based on TOH case definition and not by PFGE isolate typing.

Our study results showed that 52% of MRSA cases were male, with no significant difference in the gender distribution between CA-MRSA and HA-MRSA cases. Nichol et al (2013) reported that 58.5% of

the isolated MRSA strains were from male patients and there was not a significant difference between the two genotypes regarding the gender distribution.[7] The small difference in results between the two studies may be explained by classification of MRSA infection type. In our study it was TOH case definition without laboratory confirmation of the genotype as in Nichol et al (2013) study.

Based on data collected for our study, there was no significant difference between the median length of hospital stay (LOS) for the MRSA cases group (LOS=11 days) and the control group (LOS=10 days). On the other hand, the median number of days spent in ICU by MRSA cases (6 days) was significantly lower compared to the median number of days spent by the patients in control group (14 days). On the reviewed literature, the median LOS for MRSA patients can vary between 7 and 27 days. Datta et Huang (2008) found that the median LOS among MRSA inpatient was 7 days.[63] Potashman et al (2016) examined LOS in Canada among patients with acute bacterial skin and skin structure infection caused by MRSA and found that in Ontario the median LOS was 7.7 days.[64] Cosgrove et al (2005) concluded that the median length of hospitalization for MRSA bacteremia patients was 9 days.[65] Ben-David et al (2009) showed that ICU MRSA bloodstream infection patients had a higher median length of stay after infection - 20.5 days.[66] Sligl et al (2007) determined that the median lengths of stay for ICU MRSA patients were 13 days in ICU and 27 days in-hospital.[67] The reasons for the difference between LOS from our study and the previously mentioned studies might be the study inclusion criteria which excluded younger people, the type of MRSA infection (i.e., skin infection, bloodstream infection), the severity of the infection, and cases' comorbidities. In other words, our study included people with all types of MRSA and not only bloodstream infection, for example.

In our study, there were 55 deaths (10.05%) among the MRSA cases and 38 deaths (6.95%) among the controls showing no significant difference between the two groups. Moreover, among the ICU cases, there were 17 deaths (26%) among the ICU MRSA cases and 6 deaths (20%) among the ICU control

patients with no significant difference in between the two groups. Datta et Huang (2008) found 41 deaths (15%) among MRSA positive-culture identified patients during the studied period.[63] Hanberger et al (2011) obtained an ICU mortality rate for MRSA patients of 29.1%, and the correspondent hospital mortality rate was 36.4%.[68] Our study results showed for MRSA cases a lower hospital mortality rate, and a similar ICU mortality rate compared to the studies reviewed. Reasons for the lower mortality in our study could be due to differences in the Canadian health care system and /or practices.

Furthermore, we compared the patient median Charlson Comorbidity Index between the groups. The median value of Charlson Comorbidity Index was equal to 2 for each group. McGregor et al (2005) used the Charlson Comorbidity Index to assess the comorbidity-attributable risk of nosocomial infection with MRSA, and found a similar value of 2 for the median Charlson Comorbidity Index for the MRSA cases.[69]

Based on the data provided by TOH Infection Prevention and Control Program, 58% MRSA cases were identified as CA- MRSA, 41% MRSA cases as HA-MRSA, and 0.9% cases as "unknown". Identifying the MRSA cases in our study by TOH case definition is the main reason of not being able to compare our results with PHAC's latest published patient data which used laboratory identification of MRSA genotype in CNISP hospitals.

It is interesting to mention that when we determined the reference periods for data analysis, we could not establish a pattern/seasonality in MRSA infection outbreak onset in the studied TOH campuses. As it was indicated before, the MRSA cases' data were obtained from TOH Infection Prevention and Control Program. At TOH the MRSA outbreaks have been identified at the unit level (not campus level). It is

possible that our identification of the index data (start of outbreak) for each campus would not have been correlated with outbreaks that may actually have been ongoing at the time on a given unit.

Social network analysis has been used in epidemiology as a tool to characterize the infection transmission in sexually transmitted diseases (STDs)[38, 39], tuberculosis[70] and to identify bloodborne pathogen transmission among injection drug users[78]; to model infection transmission[71-73]; to model community-based health problems related to flu[74], obesity[74] and STDs[75], and as well, to a lesser frequency, to model infection in a hospital setting[46-48, 53]. We have found only one study by Geva et al (2011) that has used network analysis and electronic medical records data to build a healthcare network connecting patient, roommate and attending nurse to show the spread of MRSA in a large tertiary NICU.[49]

Our study's primary outcome was to demonstrate the feasibility of building a network of healthcare providers (i.e., attending physicians) and places (i.e., patient room) which are connected to patients colonized or infected with MRSA in a large tertiary care facility. We were able to build the healthcare network using electronic medical records data that were then entered into a visualization network software program (i.e., Pajek). After that, we measured overall network measures (i.e., size, density) and two individual network measures for both networks (i.e., degree centrality and eigenvector centrality). Finally, we compared the median degree centrality measure between the groups and reference periods to determine if there are significant differences.

Using the network visualization method (Figures 17-19, in Chapter 4 - Results section), we were able to conclude that for each one of the study group, there were visible differences between the network's structure when compared for the two reference periods, and each TOH campus. In period 1, the networks

had an increased number of vertices (representing MRSA cases/controls, roommates, rooms and attending physicians) and lines (representing connections between pairs of vertices), and the networks were more dense in the central area compared to their periphery. These network visible changes in the number of vertices, lines and density were supported by the actual overall structure network measures (i.e., network: order, size and density) calculation.

Referring to the overall structure network measures (Table 5, in Chapter 4 - Results section), it was observed that the number of vertices and lines increased in reference period 1 compared to period 0 for both groups and each studied campus. The increase in the number of vertices and lines during the reference period 1 (outbreak) may be explained by increasing the number of rooms (represented by vertices) to isolate the increasing number of MRSA cases and moving the cases' roommates to other rooms to prevent the MRSA spread.

Also, the network density measured for period 1 showed tendency to decrease in value compared to period 0 which is in concurrence with what is known about this network measure. De Nooy et al in their book "Exploratory Network Analysis with Pajek"(Cambridge University Press, 2005) noted that the network density and network size are inversely related: "when the network increases in size, the lower the density becomes since the number of possible lines increases rapidly with the number of the vertices in the network while the number of lines each vertex can maintain is limited".[76] In conclusion, the tendency in reducing the network density in reference period 1 indicated an increase in network size (which was represented by the increase in the number of vertices and number of network's lines/connections).

The next step was to compare the calculated median degree centrality (defined as the number of lines/connections a vertex has with other vertices) for both groups' networks, and for the two reference periods. First, when comparing each group's median degree centrality for both reference periods, it was determined that there was a significant increase in median degree centrality in period 1 compared to period 0 for both groups at Civic and General Campus but no difference in median degree centrality between the two reference periods for both groups at Heart Institute campus. For Civic and General Campus, the increase in median degree centrality in period 1 compared to period 0, may be explained by the increasing number of MRSA cases, hospital rooms occupied by patients, and as well by moving patients out of the rooms where the MRSA spread was occurring (MRSA cases to be isolated and the roommates moved to clean, non-contaminated rooms) , which increased the number of connections for those patients (especially for the roommates of the MRSA cases). For the Heart Institute, both groups, the possible reason of not having a significant difference between the median degree centrality results, for the two reference periods, might be the fact that the number of network's connections did not change during reference period 1 possibly due to the initial admission of these MRSA cases/controls in private rooms thus isolating the MRSA cases from the beginning.

Second, comparing the median degree centrality between the groups for period 0, there was no difference between the two groups for all three TOH campuses. Furthermore, for period 1 there was a significant decrease in median degree centrality for MRSA case group compared to median degree centrality of control group for Civic and General Campus but no difference between these measures for Heart Institute campus.

This decrease in median degree centrality for the Civic and General Campus for period 1 may be explained by the fact that during an outbreak the MRSA cases are isolated; therefore their number of

connections with other people is drastically reduced. On the other hand, for Heart Institute, based on the results obtained, there was no significant difference between the median degree centrality obtained for period 0 and 1. Therefore, the number of connections between the network's vertices stays the same in both periods. Heart Institute campus is a small facility, with many private rooms, thus it is possible that the MRSA cases were isolated, from hospital admission to discharge, reducing the number of connections with other patients and/or moving to other rooms.

To determine the most influential vertices for the MRSA transmission in a hospital setting, degree centrality and eigenvector centrality calculated for each TOH campus's MRSA case group and the two reference periods were compared. Based on the results, it was concluded that the most influential individuals and places in the network are those with high degree centrality, and high eigenvector centrality. It was hypothesized that a vertex (individual or place) with high degree centrality would most likely transmit the MRSA bacterium if it has numerous connections with other vertices (individual or place) in the network. Also, it was speculated that those places or people which do not have many links themselves, but whose neighbours are very well connected, were also key in MRSA transmission. Based on the results, the two measures were highly correlated. To determine the most influential vertices in the networks by comparing the two centrality measures, we stratified by MRSA cases, place (patient room) and physicians. In our networks, comparing the number of connections that a vertex can have, we determined that the place (for example, Intensive Care unit) had the highest degree centrality, followed by MRSA cases (there were cases with over 100 days hospital stay, thus increased number of connections during that period), and physicians had the lowest degree centrality (highest degree centrality found for physician was 7).

For all TOH campuses, based on the two calculated centrality measures, the top 1-3 most influential MRSA cases were generally the same but sometimes the order was different. Eigenvector centrality did not add any new highly central person, thus in this particular instance could not be found the value of adding this measure. Similar results were obtained when compared the two centrality measures for the patient rooms, for all studied campuses. However, there was not a correlation between the two centrality measures calculated for the physicians.

In conclusion, based on our results, it was possible to find patients and rooms that may be considered "influential" in the hospital network, in MRSA transmission during the study period. Even though, there were attending physicians that had a high degree centrality (i.e., Z255 - DC=7), all of them had a very low eigenvector centrality (i.e., zero or close to zero). These findings may be explained by the fact that physicians were connected with very small number of patients (highest degree centrality for physicians was 7), and majority of these patients were not very well connected (not influential) in the network. Moreover, based on our results, there is the chance that attending physicians were a potential vector of MRSA transmission for a limited period of time (there was no one physician identified who was connected with MRSA cases in both reference periods).

To better illustrate the importance of certain vertices in the MRSA infection transmission in a hospital setting, we created a dynamic animation of the Heart Institute MRSA cases' network for the two reference periods. Four patients and three places were chosen to be followed during the reference periods in this "movie". The MRSA cases chosen to be followed were patients with an increased length of hospital stay (e.g., over 68 days), admitted into the hospital during the pre-outbreak period/before this period, and had first MRSA positive lab test report confirmed during the pre-outbreak period/before it. The places chosen

were included in the cases' network starting pre-outbreak period and they were connected with the chosen MRSA cases.

The dynamic animation showed that certain individuals (e.g., MRSA case #43) and places (e.g., H1CA, HCSA, HCSB) may be considered as potential sources of MRSA transmission during the reference periods.

Finally, based on the study's results it can be concluded that it is feasible to build a social network of healthcare workers and places connected to MRSA patients in a large tertiary care hospital based on electronic medical records data. The network changes were supported by known hospital patient movements after outbreak onset (e.g., moving MRSA positive cases and their roommates to other rooms). In addition, the network measures (e.g., network size, density, degree centrality) reflected network changes during the outbreak. Also, we were able to identify individuals and places that might be the sources for the MRSA spread in the large tertiary acute-care hospital. Moreover, the network measures defining the most influential person and place in the network were highly correlated. However, it was not possible to determine the healthcare workers role in the MRSA transmission in the hospital's network due to limitations in data collection (e.g., not all healthcare workers included in the network), and the network measures chosen for analysis (e.g., eigenvector centrality).

5.2. *Limitations*

There were several limitations with the social network analysis (SNA) in this study. First major challenge for this analysis was gathering accurate and complete data for building the networks. Initially, we planned to include into the network not just the patient, patient room(s), patient roommate(s) and attending physician(s) but all healthcare providers (i.e., resident physicians, nurse, x-ray technician, etc) with whom the patient had encounter(s) and the other places visited by patient during the hospital stay. Part of this data was not captured into TOHDW and part of it could not be collected. However, even though the healthcare networks built in this study did not include all the individuals and places, we consider that our results are valuable. The social networks constructed for our purpose may have been more robust had data been available from a fully integrated hospital electronic medical records in which documentation of healthcare providers and details of other patient interactions would be more accurate, more comprehensive, and perhaps more readily extractable.

The second major challenge was the absence of well defined network measures to be used in characterizing the MRSA transmission in a healthcare network, especially in a hospital setting network. We have chosen the two network individual measures based on the best literature available.

The third limitation was the "rigid" way of collecting data for the part of the network's vertices (MRSA patients, and their roommates). We were not able to show in our networks patient's connections (i.e., transfer) between the three campuses - part of TOH. As well, we were not able to show in our networks if a roommate who came in contact with an MRSA case became an MRSA case later on, as well.

Fourth, in this study we did not include a subgraph analysis which might be provided additional valuable information to support our primary outcome. Since this was a feasibility study, we considered using just the visualization and network descriptive properties analysis methods.

Finally, it was hard to interpret the SNA results combined with the traditional statistical analysis methods (i.e., non-parametric tests) since to our knowledge, based on the literature reviewed, there are no other reference studies to be used to compare to our study results.

5.3   Conclusions

This study showed that social network analysis (SNA) can be used to build a healthcare network in a hospital setting based on electronic medical records data. Even though our networks did not include all the individuals with whom the patients had interactions during their hospital stay, we proved that SNA can be a useful epidemiological tool that can help to better understand the dynamic transmission of MRSA in a hospital setting. Being able to identify the individuals and places in the hospital that may facilitate the MRSA spread can assist the hospital's Infection Prevention and Control Program in finding the right targets for applying or enhancing existing preventive measures (i.e., hand washing, decolonization, room disinfection, etc) with the goal of reducing MRSA transmission. In addition, visualization and animation of a network is a very efficient way of representing the information about the relations among individuals and places in a hospital's network. Further study using SNA in real time is required in order to demonstrate whether this method can augment current practices for outbreak management, and minimize the impact of an infectious disease outbreak within a healthcare setting.

This thesis represents an important contribution to the current literature as it brings valuable knowledge on building a healthcare network based on electronic medical records data in a hospital setting (i.e., large tertiary acute-care facility). Since current literature lacks studies testing SNA in a hospital setting by using electronic medical records data, further and in more depth research is required to verify/dispute these study findings. We have in mind interesting future projects to test SNA including (1) continuing to explore the data obtained from TOHDW (i.e., to do a subgroup analysis, try to connect the nurses to existing networks, finding new network measures that can help define different aspects of MRSA transmission), (2) finding more applications for network visualization and animation in infectious disease epidemiology, and (3) exploring the use of SNA in representing MRSA genotype circulating in a hospital setting or comparing their circulation in different areas of the country or in different parts of the word.

Network terminology

Edge, line, tie

Component 2

6

Ego

Alters

Isolate

Node, actor, vertex

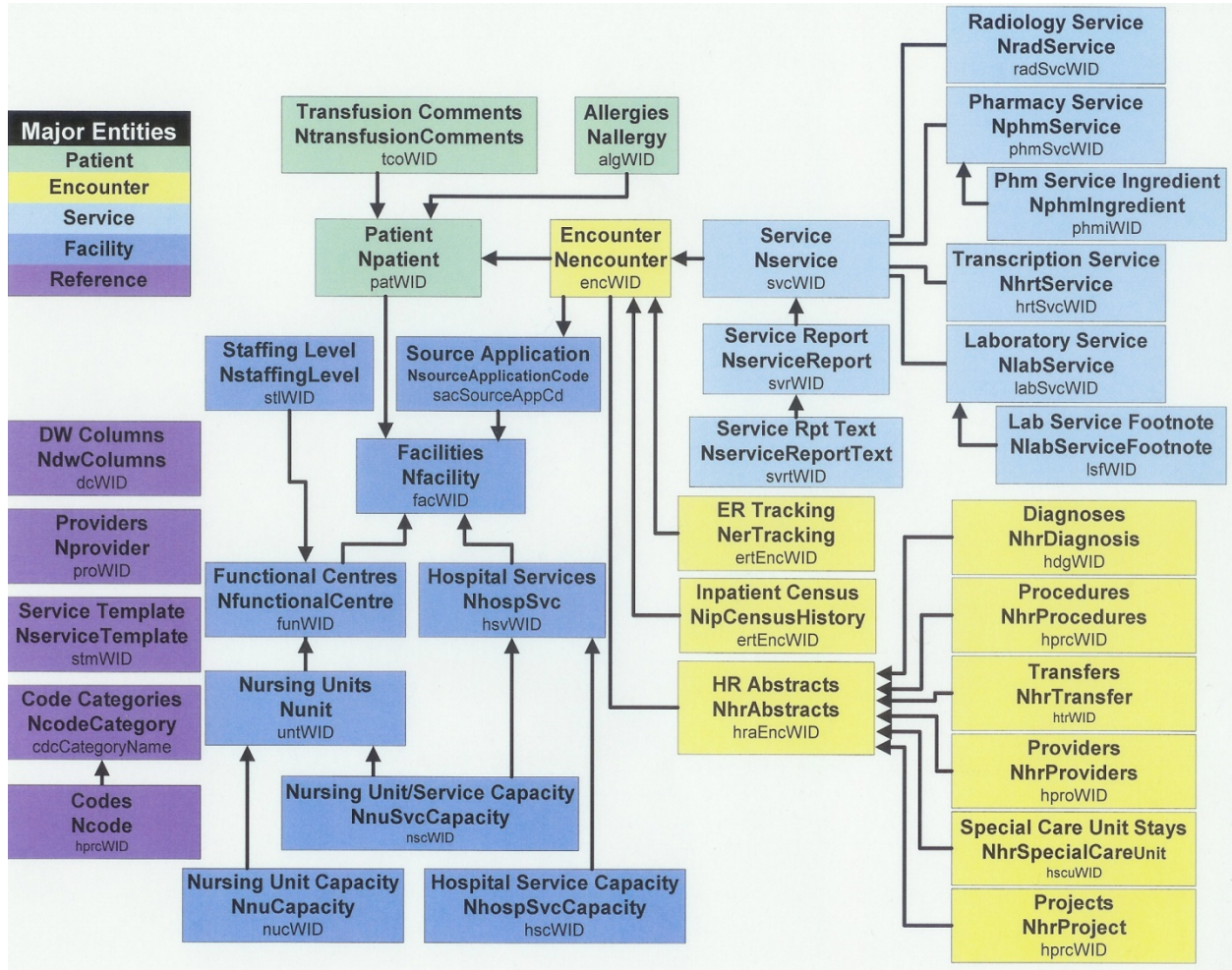**Component** is a graph or part thereof in which all the nodes are connected by a path o any length

Component 1
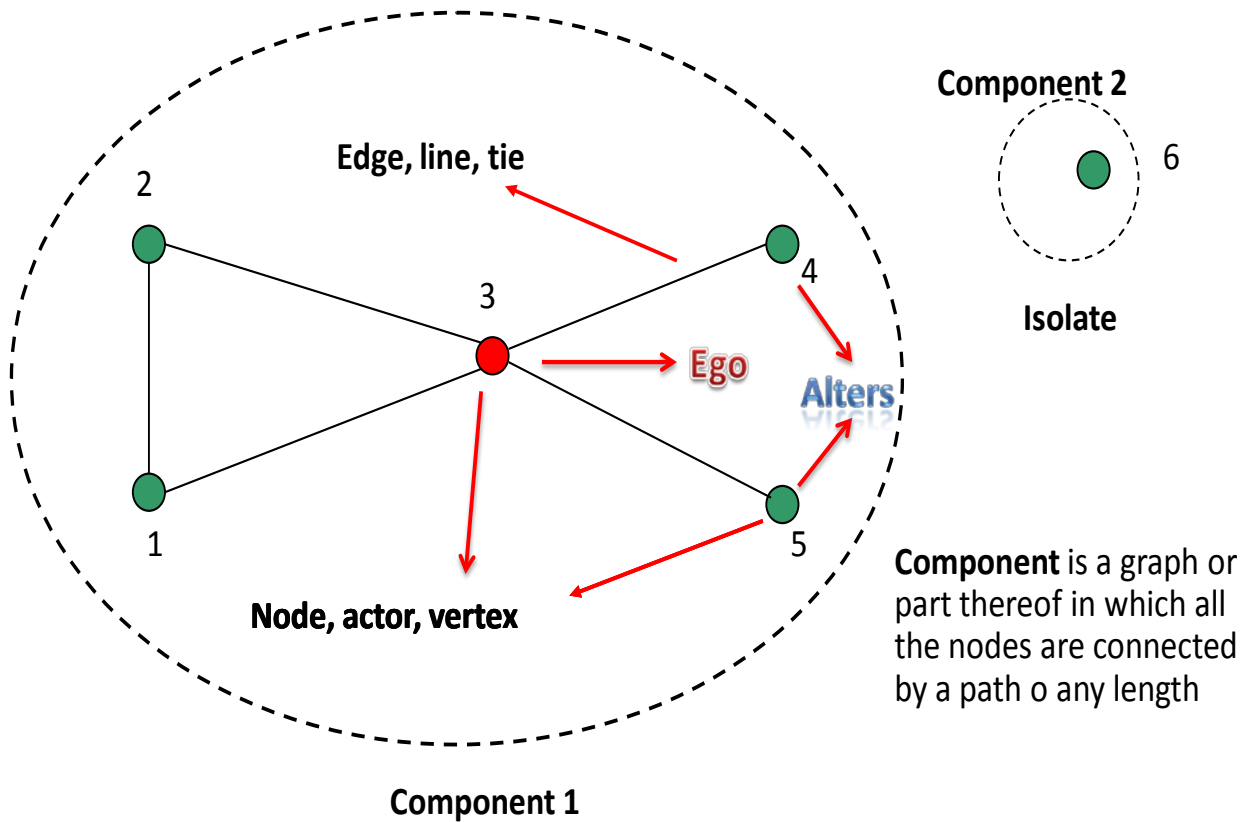
Appendix B

DIAGRAM OF THE OTTAWA HOSPITAL DATA WAREHOUSE

Appendix C

Data Specification Form

Protocol title	Network Analysis of Methicillin-Resistant Staphylococcus Aureus Spread in a Large Tertiary Care Facility
REB URL	https://mytoh.ottawahospital.on.ca/irisapp/eREB_App/Part1.aspx?FormID=3452 &FID=1a14a02a-c988-46e7-928a-5b1f2d84726f
Principal Investigator	Ann Jolly, Kathy Suh
Requestor	Ioana Doina Moldovan
Important external deadlines	

Is this an amendment to a previously approved Data Request? ☐ Yes (If yes, please provide REB number)

* Greyed out sections to be filled in by Performance Measurement/Health Records.

CA Service Request ID	4519
Analyst assigned	Erin Liu

A. Cohort Definition

This cohort definition will be used to assess the feasibility of the data request as well as to derive the data specified in section B (Data Table Request). The data source will be determined by Performance Measurement/Health Records staff. The number of records will typically only be filled in by Performance Measurement/Health Records staff during the product preparation phase (after REB approval).

Verbal description of cohort	All positively identified MRSA cases plus age-group matched controls
Start/End Dates	In hospital Apr 1, 2013 – Mar 31, 2014

	Inclusion/Exclusion Criteria (in order to be applied)	Data Source	# Records
Case Definition			
1.	Cases will be provided as an MRN list (Excel format) from Infection Control database. Variables in Excel file will include: a) **MRN b) Admission date c) Discharge date d) Test taken e) Campus f) Location get infection (attributed location) g) IC alerts (first incident of MRSA) h) Type (of infection) i) Source of infection (HA or CA-MRSA) j) Risk factors	Cerner Millennium	~600
2.	EXCLUSION: MRN not linkable to valid inpatient encounter in DW		
Control Definition			
3.	All inpatient encounters that were in-hospital during study period and: a) Who screened negative at admission and did not test positive at any point during their encounter	SMS	

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	OR b) Any roommates of an incident case who tested negative *Controls will be age-group matched to each case on a 1:1 matching		
4.	EXCLUSION: Controls that were a case at any point during study period		

Final # Records	

B. Requested Data Table(s)

- Repeat as needed for multiple tables.
- Shaded areas can be completed as much as possible (using information from <u>OHDW Database Map</u>), but will be finalized by Performance Measurement/Health Records staff.
- Columns should include all necessary "concepts" required to complete the analytical plan (e.g. age, sex, mortality, comorbidities, etc.). Be sure to include record / patient identifiers, date/time attributes, and other derived or non-derived concepts.
- **High risk fields containing sensitive PHI (Patient/Physician identifiers, birth date, postal code, textual reports possibly containing identifying information, etc) are to be identified using a double asterisk preceding the column label

Table name	Dataset 1: Cohort characteristics
Each row represents	One patient (index visit)
Filter	Cases and controls

** High risk fields containing sensitive PHI are denoted by double-asterisks

	Column label	Description and derivation details	Variable name	Data Source
1.	Encounter ID	De-identified	encWID	SMS
2.	Patient ID	De-identified	encPatWID	SMS
3.	**MRN	Not provided to researcher. Only used to link to Infection Control data	encMRN	SMS
4.	**Postal code		hraPostalCd	
5.	Age at admission	Calculated using patient's birth date	admitAge	SMS
6.	Gender		encPatGenderCd	SMS
7.	Encounter Start		encStartDtm	SMS
8.	Encounter End		encEndDtm	SMS

9.	LOS	Patient LOS in days	derived	SMS
10.	Number of Days in ICU	Number of days in ICU	hraIcuDays	NhrAbstract
11.	Admission Type	Recode SDA's to be Elective so campus coding is consistent	encAdmType	SMS
12.	Transfer Institution	Institution the patient was transferred from	hraTransferedFromInstitution	NhrAbstract
13.	Campus		encCampusCd	SMS
14.	Charlson comorbidity score	Calculated from %comorbid macro. Comorbidities based on encounter, not patient (ie: no lookback)	CharlsonScore (derived)	DAD
15.	CMG	CMG code and description	hraCmgCd_	DAD
OUTCOMES				
16.	Died	If NotInDAD=0 then hraExitCd = (07, E). Else if NotInDad=1 then encDeathInd = D	Death_flag	SMS and DAD
17.	Discharge Disposition	(e.g. discharged home, transferred, etc)	hraExitCd_	DAD
18.	Outcome status	Case or Control	derived	
19.	Infection Source	For cases, source of infection (HA or CA-MRSA)	InfectionSource	Cerner Millennium
20.	Test date	For cases, variable "Test taken". For controls, labSpecimendtm	TestDate	Cerner Millennium and NlabService

Table name	Dataset 2: Patient / Room (Unit) pairs
Each row represents	Patient stay in a room
Filter	Admissions included in cohort

	Column label	Description and derivation details	Variable name	Data Source
21.	Encounter ID	De-identified	encWid	
22.	Room	Derived		
23.	Unit		NursSta	SMS
24.	Primary Activity of Unit	Primary activity of the unit. Eg Ward, ICU, Stepdown, ED, etc		
25.	Unit Size	# of Budged and open Beds on that unit		
26.	Start Date/time	Start of patient stay in room. If multiple stays in the same room there will be multiple rows with each start/end date/times.		
27.	End Date/time	End of stay		

Table name	Dataset 3: Patient / Attending Provider pairs
Each row represents	Patient / provider pair
Filter	Admissions included in cohort

	Column label	Description and derivation details	Variable name	Data Source
1.	Encounter ID	De-Identified		SMS
2.	Attending Provider ID	De-identified		
3.	Provider Division	Division of the attending provider		
4.	Start Date/time	Start of patient being attended by the provider.		
5.	End Date/time	End of patient being attended by the provider.		

Table name	Dataset 4: Patient / Roommate pairs
Each row represents	Patient / roommate pair
Filter	Admissions included in cohort

	Column label	Description and derivation details	Variable name	Data Source
1.	Encounter ID	De-identified		SMS
2.	Room/Unit			
3.	Roommate ID	De-identified		
4.	Start Date/time	Start Date/time of Room sharing		
5.	End Date/time	End Date/time of room sharing		

Table name	Dataset 5: Unit / Nurse pairs
Each row represents	Nurse shift
Filter	Nursing shifts on units with an included admission present

	Column label	Description and derivation details	Variable name	Data Source
6.	Nurse	De-identified		
7.	Unit			
8.	Start Date/time	Start of nurse shift on unit.		
9.	End Date/time	End of nurse shift on unit.		

Table name	Dataset 6: Interventions
Each row represents	Principle intervention
Filter	Any cohort member who had a procedure

	Column label	Description and derivation details	Variable name	Data Source
1.	Encounter ID	De-identified	encWID	SMS
2.	Patient ID	De-identified	encPatWID	SMS
3.	Intervention Code	CCI code	hprcCd	NhrProcedure
4.	Intervention Code description		hprcCd_	GrouperHx
5.	Date and time	Date and time of the intervention episode start	hprcDtm	NhrProcedure
6.	Duration	Duration of episode in minutes	Derived	
7.	Provider		hprcProWID	NhrProcedure
8.	Provider Division	Provider Division, linked by proWID	proDivision	Medical Affairs
9.	Intervention Location	Location where the intervention episode took place. Eg Main OR, Endoscopy suite, ER, Delivery room, etc	hprcOperatingRoomNum	NhrProcedure

Table name	Dataset 7: Services
Each row represents	One service
Filter	XRAY services performed for included admissions

	Column label	Description and derivation details	Variable name	Data Source
1.	Encounter ID	De-identified	encWID	SMS
2.	svcStmWID	Service code	svcStmWID	NService
3.	Type of service	Type of service	svcTableCd	NService
4.	Performing service date	Date and time when service was performed	svcPerformedDtm	NService
5.	Performing service person	The person who performed the service	svcPerformedBy	NService
6.	Performing service ID	The person who performed the service	svcPerformedByUID	NService
7.	Ordering person	Who ordered the service.	svcOrderedBy	NService
8.	Ordering person ID	Provider ID	svcOrderedByProWID	NService
10.	Ordering Provider Division	Ordering Provider Division, linked by proWID	proDivision	Medical Affairs

9.	Radiologist	Radiologist (not consistently populated)	radRadiologistProWid	NradService

C. Cost estimate

The following is an estimate based on the data requirements outlined herein. This estimate is subject to change if the data requirements change.

The rate of for analyst costs are based on the OHRI Clinical Research Salary Scales for Data Management, Statistical and IT Service Cost Recovery Rates.

Costs for chart pulls completed by Health Records are based on the Health Data & Information Service Fee Structure.

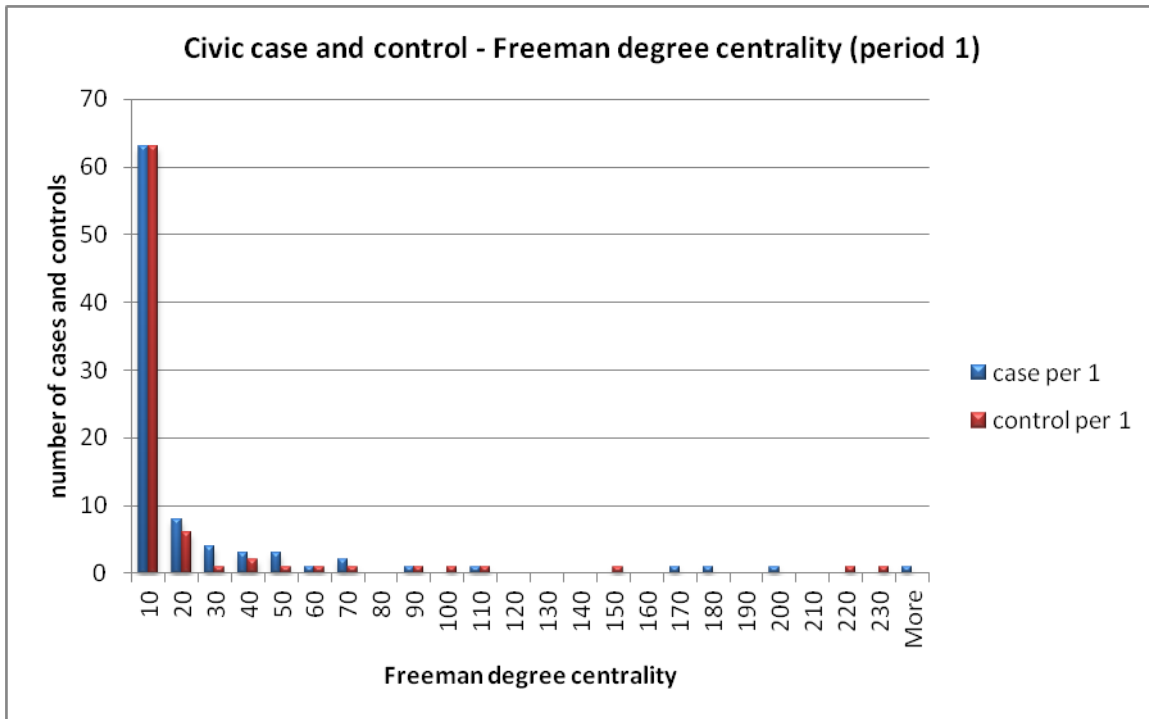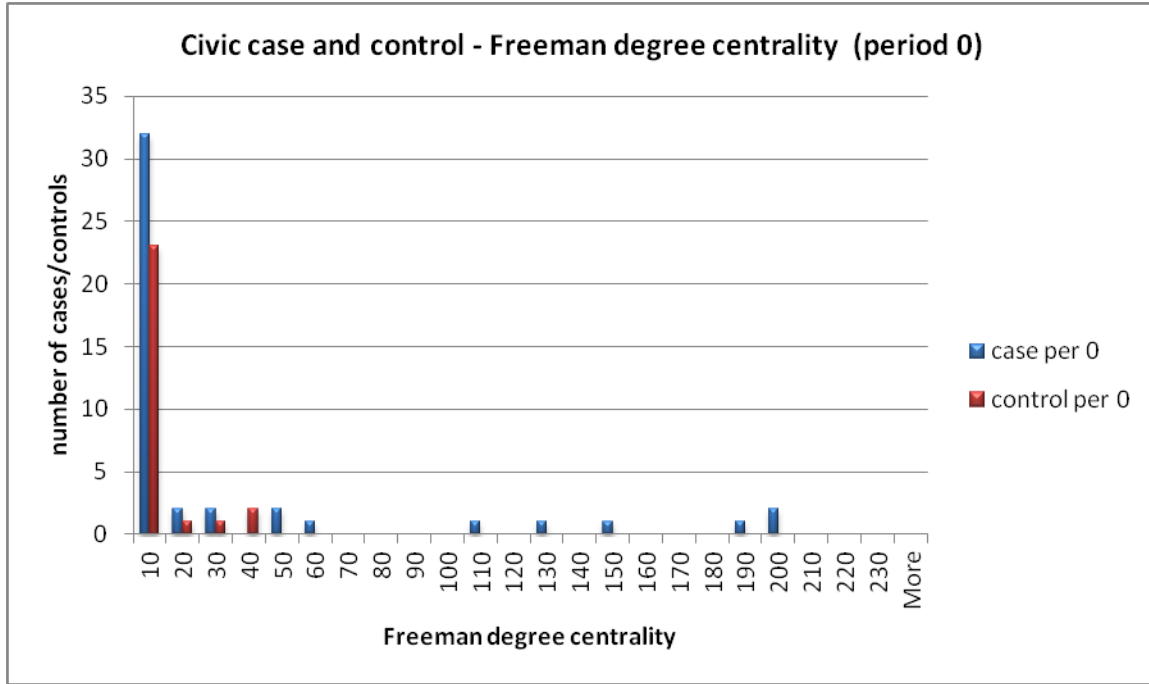|	Hours	Rate / Hr	Cost
Analyst costs (Documentation, Data Querying, QA, Analysis, Delivery)	92	$75	$6,900.00
Chart pull costs	N/A	N/A	

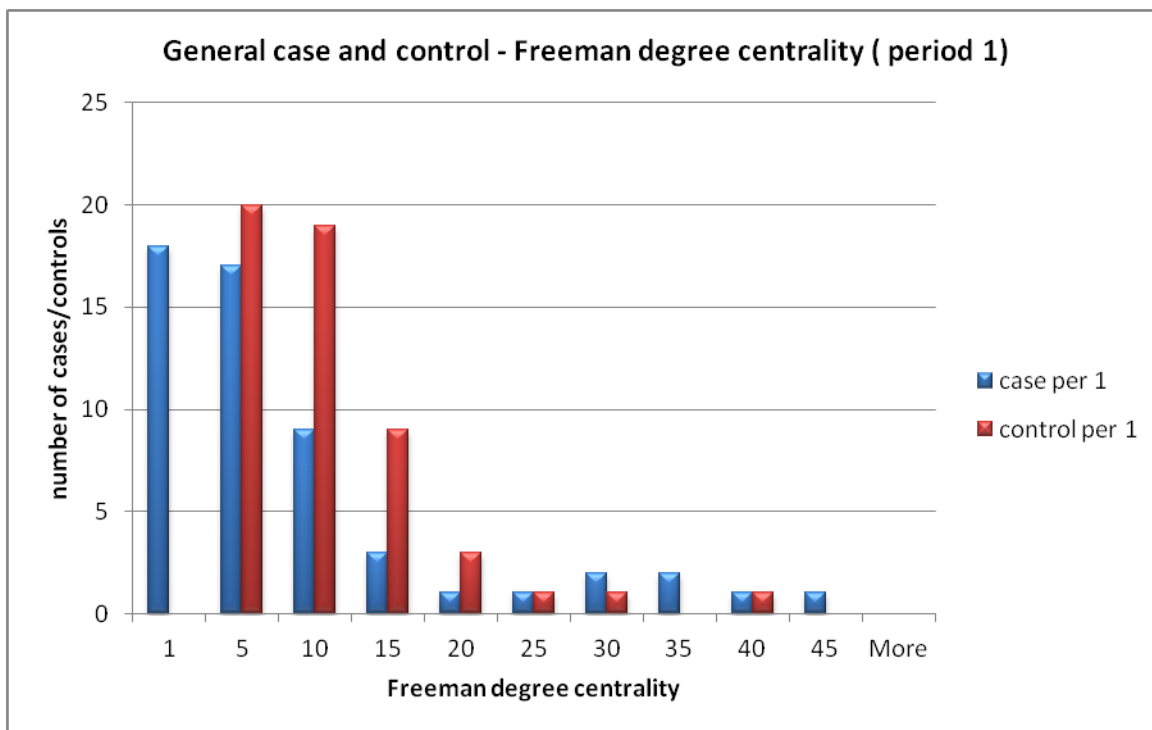*Enter hours then right click on Cost and select "Update Field" to update the cost calculation*
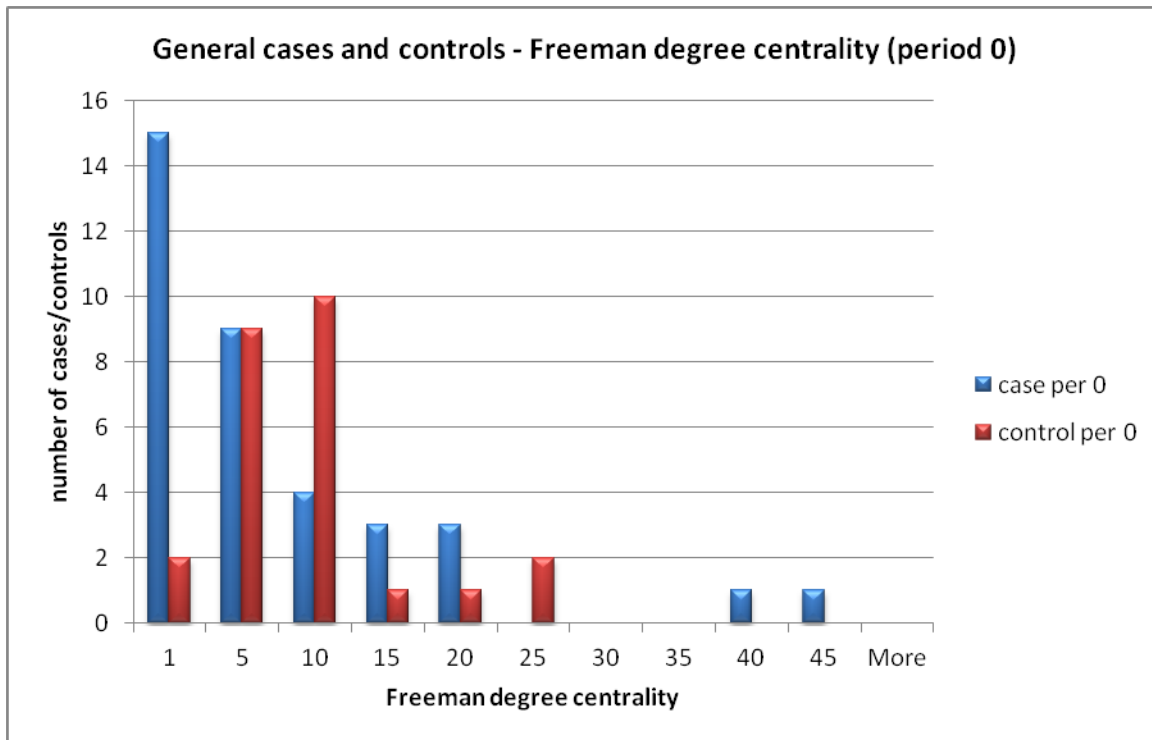
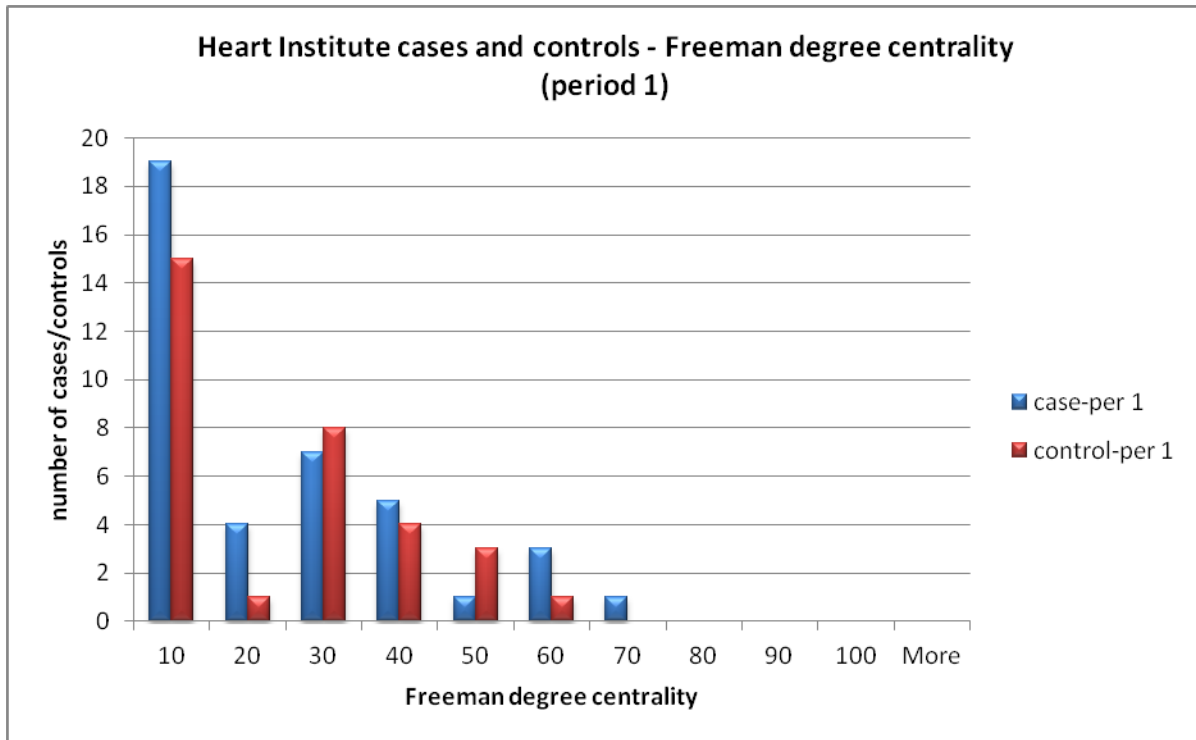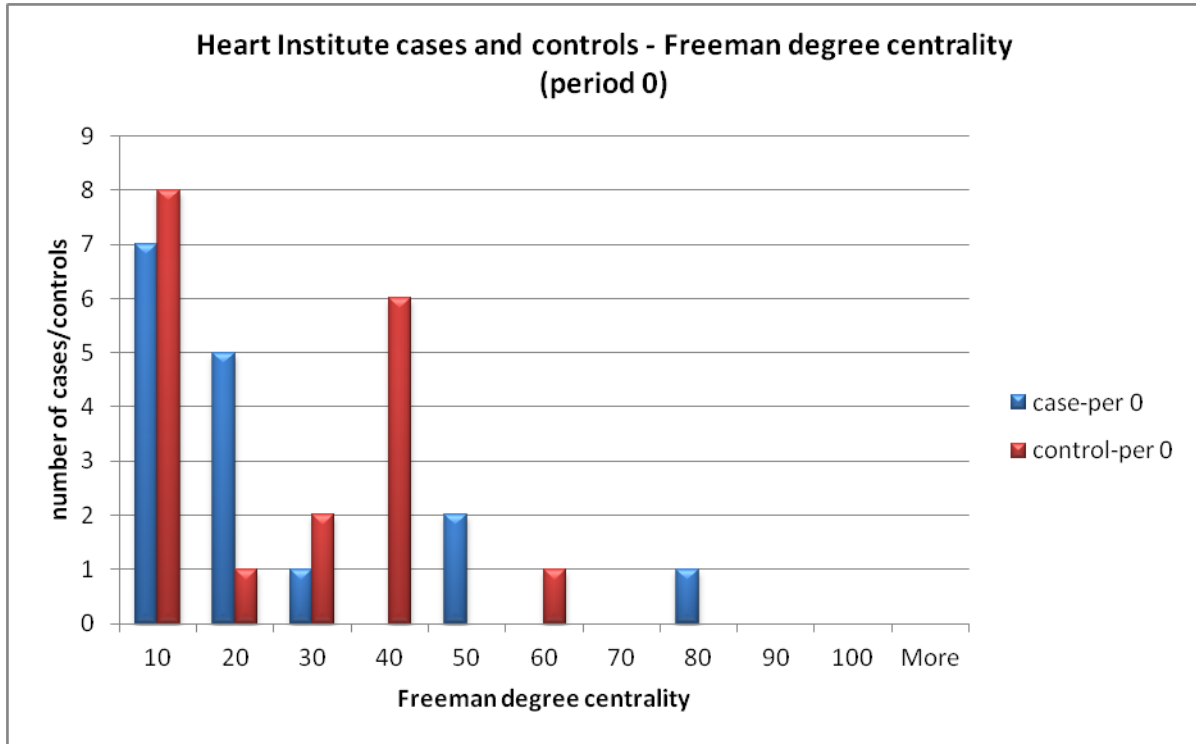**Additional details:**

Investigative	Data feasibility assessment made by Deanna	6
	Communication/meetings between analysts and researchers (This includes several email threads, 1 phone meeting, in-person meetings between the analyst and researchers, and meeting with Infection control to review the Cerner Millennium database)	6
	Consulting on external database (CNISP)	1
	Initial investigation of requirements (This includes DSF creation and amendment, reviewing prior validation work on MRSA, reviewing variables in the data warehouse and previous case definitions)	8
Data Preparation	Import MRN case list from Cerner Millennium (Excel documents) and link to valid encounter in DW	10
	Identify age-group matched controls	10
	Pulling data for Encounter characteristics (Table 1)	5
	Create and Q/A table for Patient/Room pairs using data from Inpatient Census History table (Create room definitions based on Le's criteria for CDIFF project)	6
	Retrieve data on Room/Unit characteristics	2
	Create and Q/A table for Patient/Attending provider pairs using data from Inpatient Census History table	5
	Create and Q/A table for Unit/Nurse pairs	8
	Create table of Interventions (link to ProWid table and OR Room descriptions)	3
	Create and Q/A table for Patient/Roommate pairs	5
	Retrieve all radiology services for cohort, with associated variables	4
	Further communication between analysts and researchers (ie: resolving data anomalies)	3
	Final Q/A of data	5

Appendix D

Freeman degree centrality Histograms

Civic case and control - Freeman degree centrality (period 0)

Civic case and control - Freeman degree centrality (period 1)

General cases and controls - Freeman degree centrality (period 0)

General case and control - Freeman degree centrality (period 1)

Heart Institute cases and controls - Freeman degree centrality (period 0)

Heart Institute cases and controls - Freeman degree centrality (period 1)

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