DEVELOPMENT AND DEPLOYMENT OF A
HEALTH INFORMATION EXCHANGE
TO UNDERSTAND THE TRANSMISSION OF MRSA
ACROSS HOSPITALS VIA MOLECULAR GENOTYPING
AND SOCIAL NETWORKING ANALYSIS

DISSERTATION

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By

Yosef M. Khan, MD, MPH

Graduate Program in Public Health
The Ohio State University
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Dissertation Committee:

Kurt Stevenson, MD, MPH, Advisor

Philip Binkley, MD, MPH

Melanie Brodnik, PhD

Amy Ferketich, PhD

Shu-Hua Wang, MD, TM & MPH
Abstract

**Background:** Methicillin Resistant *Staphylococcus aureus* (MRSA) is a hardy and extremely virulent multidrug resistant organism that has been a major cause of hospital acquired infections ever since its discovery in the 1960’s. It has severe consequences such as causing increased hospital length of stay, economic burden, morbidity, and mortality. MRSA prevention strategies have been advocated by national and international organizations which have been successful in reducing the burden of healthcare-associated MRSA. However, MRSA has been increasing in the community settings and this is an alarming and poorly understood rend because these infections occur in populations that have no known risk factors. In order to develop successful control strategies for this emerging threat. In order to develop successful control strategies for this emerging threat, it is important to understand the epidemiology, risk factors and links associated with community associated MRSA so that new and novel prevention strategies, using existing resources and cutting edge technology, can be developed.

**Methods:** A cross sectional observational study design was used. The aims were accomplished by leveraging and utilizing the existing infrastructure of the OSUMC Information Warehouse, the Ohio State Health Network, and the OSUMC Microbiology Laboratory. Specific aim 1 was to develop an infection control collaborative and an innovative cross institutional platform, using existing information technology resources and infrastructure, for use as an electronic health information exchange between multiple
hospitals spread across a large geographic area. Specific aim 2 was to estimate the proportion of community associated MRSA cases among all MRSA cases in rural community hospitals, and to identify the risk factors associated with community associated MRSA. Logistic regression was used to examine risk factors for community MRSA strain. Lastly, specific aim 3 was to identify patterns of intra-facility and inter-facility transmission of MRSA by evaluating epidemiological and geographic links via use of geographic information systems and social network analysis.

**Results:** An infection control collaborative among the Ohio State University Medical Center and 7 rural outreach hospitals was formed with the successful development and deployment of a health information exchange for MRSA. Over a 1 year time period from March 2009 – March 2010, 1024 MRSA isolates were collected, 625 from the OSUMC and 399 from the 7 outreach hospitals. The proportion of community associated MRSA in rural hospitals was 85%, while it was only 26% at the OSUMC (p-value < 0.001). A risk factor analysis found that age was a significant (p-value = <0.001) predictor of community associated MRSA (OR 0.92, 95% CI 0.90 – 0.94; p< 0.001). Rep-PCR testing found 75 distinct clusters. All clusters were examined for potential patterns of intra and/or inter-facility transmission. Two rep-PCR patterns, 29 and 101, provide vivid illustrations of potential transmission links.

**Conclusions:** Using surveillance to understand the transmission of MRSA is critical in infection prevention and control activities. Using health information technology is necessary to safely, effectively and efficiently treat patients and prevent outbreaks. By utilizing and enhancing existing resources, protocols, and information technology infrastructure health information exchanges can be developed. Novel methods including
SNA and GIS should be further explored to provide an in-depth understanding of the transmission patterns of MRSA within and between facilities, regional geographical variations, and national trends. This increased understanding can then be used to plan and implement effective prevention programs that respond to local and regional trends.
Dedication

Dedicated Fisabilillah to all those who strive in the path of Allah for no other reason than to please Him, have God-consciousness in their heart and actions, and aim to be the foremost of the foremost.

May Allah make you truly successful.
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Vita

2001................................................................. M.B.B.S. Medicine, Surgery
Dow Medical College

2003 – present.................................................. Research Scientist
Chemical Abstracts Service,
Columbus, Ohio, USA

2004 – 2005....................................................... Graduate Research Associate,
The Ohio State University

2005................................................................. Masters in Public Health,
The Ohio State University

2005 – 2006....................................................... Clinical Research Coordinator,
The Ohio State University

2006 – present................................................... Clinical Research Manager,
The Ohio State University

2010 – present................................................... Lecturer
The Ohio State University

PUBLICATIONS


FIELDS OF STUDY

Major Field: Public Health

  Specialization: Epidemiology

Minor Field: Health Information Management Systems

  Medical Informatics
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Chapter 1: Introduction

1.1 Statement of Problem

For thousands of years bacterial infections have been a major cause of death in the world (Forrest 1982). Cultural and homemade treatments and remedies from honey to herbs existed and were frequently, yet on a small scale, beneficial. However, it was not until the discovery of antimicrobial agents in the mid 1800’s and their mass production in the early 1900’s that societal progress in the treatment and prevention of bacterial infections gained strength. With the discovery by Fleming of penicillin in 1927, and its rampant use in the treatment of *Staphylococcus aureus* (SA) infections, also came the overuse and abuse of penicillin (Jeśman et al., 2011). By 1959, the majority of SA infections were resistant to penicillin, thus leading to the discovery and use of methicillin as the drug of choice for SA infections. However, within a couple of years of its introduction, methicillin resistant SA (MRSA) was discovered. Ever since, MRSA has become a significant multidrug resistant organism (MDRO) that has increased to epidemic and endemic levels. It is regarded as the most common healthcare-associated infection (HAI) (Chambers, 2001). MRSA has been a formidable foe over the past couple of decades as it accounts for more than 278,000 hospitalizations and 56,000 septic episodes annually (National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, 2004, p 470). It has been the focus of countless campaigns and prevention strategies due to its high mortality and morbidity.
rate. It increases length of stay in hospitals, which may result in continued transmission among patients and healthcare workers (Cosgrove et al., 2005).

It is essential to not only measure the prevalence and proportion of both hospital and community associated MRSA, but also to examine the risk factors associated with these types of infections. It is also vital to gain insights into the clonal differences within MRSA strains and how this affects the transmission of MRSA between and within regional geographic distant populations. Information technology can play a major role in gaining these insights. Therefore it is crucial to develop, utilize, and bolster current information technology infrastructure and resources to increase the ability and to allow for the easy, rapid and effective flow of healthcare information while maintaining patient privacy and confidentiality.

The purpose of this research was to develop a mechanism for the safe exchange of healthcare information, from which we can measure the proportion of community associated MRSA cases and examine the associated risk factors which allowed us to also gain an understanding of the molecular transmission of MRSA, both community associated and hospital acquired strains, across geographically distant hospitals.

This research has numerous potentially significant implications. First of all, it will test and enhance the existing information technology infrastructure by designing, creating and deploying the necessary foundations for an electronic health information exchange between multiple hospitals spread across a large regional geographic area. This will allow for the easy and safe transfer of healthcare information between hospitals. The sharing of information will augment collaboration and infection surveillance, while upholding and maintaining the regulations pertaining to patient confidentiality and privacy laws. This is
an extremely important aspect, as it will bridge the information technology divide between rural and urban hospitals, and potentially opens the doors for further collaboration and exchange of healthcare information not just by hospitals but by other key stakeholders in the at-large community. It will also allow us to measure the proportion of MRSA, both hospital acquired and community associated cases, in rural hospitals, and give us a better appreciation of the risk factors involved in community associated MRSA cases. Lastly, this research may result in an increased understanding of the geospatial transmission of MRSA via different clonal types and by social means.

1.2 Specific Research Aims

1. To develop an infection control collaborative and an innovative cross institutional platform, using existing protocol, information technology resources and infrastructure, for use as an electronic health information exchange between multiple hospitals spread across a large geographic area.

Hypothesis: It is hypothesized that by using currently available information technology resources and established Ohio State University Information Warehouse protocols, an electronic health information exchange can be designed and implemented. Thus, allowing for the easy transfer of infection control surveillance data, while adhering to patient privacy laws.

2. To estimate the proportion of community associated MRSA cases among all MRSA cases in rural community hospitals, and examine the risk factors associated with community associated MRSA.

Hypothesis: It is hypothesized that the proportion of community associated MRSA will be greater than that of hospital acquired MRSA.
3. Identify patterns of intra-facility and inter-facility transmission of MRSA by evaluating epidemiological and geographic links via use of geographic information systems and social network analysis.

Hypothesis: It is hypothesized that distinct molecular clones of MRSA will be isolated and transmission of these clones between communities and facilities will have occurred based on geographic and social links.
Chapter 2: Background

2.1 *Staphylococcus aureus*

Since its isolation and discovery in 1880, by Scottish surgeon Alexander Ogston, (Ogston A, 1884) *Staphylococcus aureus* (SA) has been one of the most widely studied (Deurenberg and Stobberingh, 2008) and commonly treated bacterial infections (Ryan and Ray, 2003, P. 261).

*Staphylococcus aureus* is a member of the *Staphylococcus* genus and the *Micrococcaceae* family (Joklik et al., 1988, p.344). It is a non-spore forming, non-motile, gram positive coccus that measures approximately 1 micrometer in diameter. It is structured in grape like clusters and can grow in both anaerobic and aerobic conditions, but flourishes under the latter (Davis et al., 1990, p.540). Under aerobic conditions, catalase is produced thereby forming acid, while under anaerobic conditions manitol is fermented. In fact, SA is the only *staphylococcus* species to be able to ferment manitol. Figure 1 depicts SA under an electron microscope.
Culture on blood agar produces golden colored colonies surrounded by numerous hemolytic zones (see figure 2.2) with production of up to four different types of hemolysins (α, β, γ, δ hemolysin). SA is one of the most vigorous non-spore forming bacteria, as it can live for months on agar plates and is often found in older dried samples of pus (Davis et al., 1990, p.540). It also has a high salt tolerance and thus can be grown on media containing 7.5 – 10% NaCl.
The bacteria itself is structured much like other gram positive bacterium (Ryan and Ray, 2003, P. 261). It consists of a cell wall made up of the peptidoglycan murein. Murein is composed of N-acetyl-glucosamine and N-acetylmuramic acid, both sugars, interlinked to each other to form a linear glycan chain. It is this chain that extends around the entire cell wall of SA, thus creating a protective molding giving SA its hardiness. Interspersed within the peptidoglycan layer are molecules of ribitol-techtonic acid, an antigenic specific to SA (Ryan and Ray, 2003, P. 261). These acids can cause activation of the alternative pathway in the complement system, thus causing macrophages to secrete certain cytokines. Since SA is a prokaryotic cell it does not have a true nuclei but instead keeps it DNA in a nucleiod (Brooks et al., 2010, p. 13.). Figure 3 depicts the cellular structure and components of SA.
SA is part of the normal flora of human skin and mucous membranes. In a study published by Miller et al. (2009), the authors found that up to 25% of all individuals and 40% of all households may persistently be colonized with SA. It is estimated that up to 80% of individuals will be colonized at some time or another (von Eiff et al., 2001). The most common site of colonization is the anterior nares. Other potential sites of colonization include the throat, (Mertz et al., 2009) axilla, rectum, and perineum. Colonization, without infection, represents a stable interaction of SA cellular adhesins such as laminin, fibronectin, and collagen to mucous membrane receptors (Davis et al., 1990, p.540).
Virulence is the measure of the ability of bacteria to cause an infection, and thus bacterial infections are caused by internal virulence factors (Baron, 1996). Virulence factors are small molecules secreted by bacteria that are responsible for causing disease. They enable the bacteria to evade and inhibit the host’s immune system. SA utilizes several virulence factors such as invasions, surface proteins, biochemical properties that enhance their survival in phagocytes, membrane-damaging toxins that lyse eucaryotic cell membranes, exotoxins, and most importantly the evolution into a multi-drug resistant organism. Invasins such as hyaluronidase, an enzyme that destroys the polysaccharide layer which holds animal cells together, make it easier for the bacteria to spread through the tissues of the host organism. Surface proteins inhibit phagocytic engulfment, a process that is needed to rid cells of foreign elements. One such protein in SA is Protein A, an IgG-binding protein that binds to the Fc region of the antibody IgG thus preventing correct binding of opsonizing antibodies, which in turn hinders phagocytosis (Kayser et al., 2004). One important biochemical property in SA that improves the survival in phagocytes is the production of catalase. Catalase converts hydrogen peroxide hydrogen (H$_2$O$_2$) to water and oxygen thereby protecting the cell. It is thought the purpose of catalase in the bacterial cell may be to protect it from hydrogen peroxide mediated leukocyte bactericidal mechanisms (Mandell, 1975). Hemolysins are toxins that lyse the cell membranes of mainly eucaryotic cells, such as human cells. The most common hemolysin, $\alpha$-hemolysin causes inflammation by inducing the secretion of pro-inflammatory cytokines IL-1$\beta$ and IL-18 which in turn causes pores to form in the cell membrane (Craven et al., 2009; Bantel et al., 2001). SA produces several exotoxins that
can damage host tissue or cause systemic disease (Dinges et al., 2000). Two of these exotoxins are toxic shock syndrome toxin 1 (TSST-1) and exofoilative toxin (ET).

Toxic shock syndrome toxin 1 is produced in roughly 1% of SA isolates. It is a super antigen that induces pyrogenicity, superantigenicity, and the ability to induce fatal hypersensitivity to endotoxin (Bohach et al., 1990) and causes an often lethal syndrome characterized by a high fever, diffuse erythematous rash, desquamation of the skin, and multiple organ system failure. It is also has the special ability to cross mucosal surfaces (Bohach et al., 1998). Exofoilative toxins are responsible for producing staphylococcal scalded-skin syndrome (SSSS) which is a blistering skin disorder mostly seen in children (Ladhani et al., 1999).

SA causes a variety of infections and disorders. It is a major cause of skin and soft-tissue, respiratory, bone, joint, and endovascular conditions (Lowy, 1998). Common infectious conditions include boils, furuncles, cellulitis, wound infections, abscesses, septic and toxic shock (Kumar and Clark, 1998). It is also an important cause of bacteremia and endocarditis (Lowy, 1998). According to a study published by Sanabria et al., 25% of all endocarditis cases are cause by SA (Sanabria et al., 1990), with a higher prevalence in intravenous drug users, elderly patients, patients with prosthetic valves, and hospitalized patients (Lowy, 1998). It also has a great potential to spread to other sites including the bones, joints, kidneys, and lungs (Musher et al., 1994).

The treatment of SA is either surgical or drug based. Surgical treatment includes drainage of purulent collections of pus, debridement of any necrotic tissue, and removal of any foreign bodies like intravenous lines, artificial grafts, heart valves, or pacemakers. Adequate drainage is very essential. Often in skin and soft tissue infections only drainage
and not antibiotic therapy is needed (Deresiewicz et al., 2005). The organism should always be tested for drug susceptibilities and then the appropriate antibiotic should be administered.

2.2 Emerging resistance

With its discovery in 1940, penicillin became the most widely used and effective treatment against SA. Originally derived from the Penicillium fungi (Dorland, 2000), penicillin and its sub-classes are known as bactericidal drugs. These drugs work to kill bacteria without the need or help of the host body’s immune system (Tevor and Katzung, 2005, p. 363). Penicillin contains both a thiazolidine and β–lactam ring and is derivative of 6-aminopenicillanic acid. Structural integrity of the 6-aminopenicillanic acid nucleus is vital to penicillin maintaining its antimicrobial properties (Katzung, 2004, p. 734). Penicillin and its sub-classes work by inhibiting the process of cell wall synthesis in bacterial cells. They achieve this by the following three steps: 1) binding of the drug to penicillin-binding protein receptors which are found within the cytoplasmic membranes of bacterial cells; 2) inhibiting the transpeptidase enzymes that are in the formation of the interlinked peptidoglycan chains of the cell wall; and 3) activating “autolytic enzymes that cause lesions in the bacterial cell wall” (Katzung, 2004, p. 734).

Resistance to penicillin occurs via the following four main pathways: 1) inactivation by the production and interaction of β–lactamase with the drug; 2) modification of the target penicillin-binding proteins; 3) impaired penetration of drugs to target receptors and; 4) and the presence of an efflux pump (Katzung, 2004, p. 734).

Prior to the discovery of penicillin, the mortality rate of SA infections was roughly 80% (Binh et al., 2006). After its use became the standard of care, the mortality
rate dropped drastically (Gorbach et al., 2004, p. 398). However, almost immediately, penicillin resistant strains of SA began to occur and increase until 1959, when most SA isolates were resistant to penicillin (Deurenberg and Stobberingh, 2008). The next line of treatment was a methicillin, a penicillinase-resistant penicillin, however by 1961, two years after its introduction, SA also developed resistance to methicillin thus sparking the current crisis and epidemic which has lasted over half a century.

2.3 Methicillin resistant *Staphylococcus aureus*

2.3.1 Emergence

Methicillin resistant *Staphylococcus aureus* (MRSA) began to emerge almost immediately after its use as the front line antibiotic against SA (Deurenberg and Stobberingh, 2008). The first resistant isolate was discovered in the United Kingdom in 1961 (Enright et al., 2002). MRSA did not appear in the United States until 1968, when it was discovered in Boston. The first officially recognized outbreak of MRSA was located in several hospitals in Eastern Australia and occurred in 1970 (Grunden, 2002). Ever since then, MRSA has increased to endemic proportions (Eseonu et al., 2011). As the proportion and worldwide locations of resistant isolates increased, so did the number of drugs that SA became resistant to and thus MRSA became known as a multi-drug resistant strain of SA. Today the term MRSA is defined as SA isolates that are resistant to all currently available β-lactam antibiotics including penicillins, cephalosporins, and carbepenems (APIC, 2010). It is and has been for scores the most common identified multi-drug resistant organism (MDRO) pathogen around the world. The percentage of MRSA isolates found in U.S. hospitals increased from 2.4% in 1975 to 29% in 1991 (Panlilo et al., 1992), and from 1992 – 2003 the proportion in ICUs increased to 59%
accounting for a 3% increase each year (Klevens et al., 2006). This trend has also been seen in countries around the world such as Canada, Germany, and Japan (Shorr et al., 2006).

The emergence and continuing incidence of MRSA provides significant challenges to the both the healthcare community and the general public, specifically in terms of cost, economic burden, treatment, prevention, and elimination strategies.

2.3.2 Mechanism of resistance and Structure

The main mechanism of resistance for MRSA is the formation of β-lactamases; enzymes that hydrolyze the β-lactam rings and thereby making the antibiotics inactive (Tevor and Katzung, 2005, p. 363). This occurs primarily by the acquisition of the mecA gene. The mecA gene codes for penicillin-binding protein 2a (PBP2a), an enzyme that has decreased affinity for β-lactam antimicrobials. In a non-resistant SA isolate, the β-lactam antibiotic binds to the penicillin-binding protein that is present in the cell wall of the bacteria. This binding then allows for the disruption of the peptidoglycan layer, which in turns makes the bacteria vulnerable and unable to hold together and withstand lyses. However when PBP2a is present it essentially does not allow the antibiotic to bind to the bacteria, therefore allowing the cell wall to synthesis and bacteria to grow by transpeptidase activity.

The mecA gene is regulated by a repressor known as MecI and the β-lactam sensing signal transducer MecR1 (Deurenberg and Stobberingh, 2008). The presence of a β-lactam antibiotic causes MecR1 to be auto-catalytically cleaved thereby activating metalloprotease which in turn cleaves a mecA bound MecI. It is the cleaving of
MecI which begins the transcription process of MecA thus resulting in the production of PBP2a. However if a β-lactam antibiotic is not present, MecI represses the transcription of mecA and MecR1-mecI.

The mecA gene is found on a portion of the staphylococcal chromosome cassette mec (SCCmec) (Daum et al., 2002). In addition to the mecA gene and its two regulators, The SCCmec also encompasses a pair of chromosomal cassette recombinase genes (ccr) that facilitate insertion and excision of SCCmec from the bacterial genome. The SCCmec is also recognized by its distinct, direct and inverted repeats at either end of the SCCmec element.

The origin of the SCCmec is not known, but studies have suggested that it is a genetically linked to other types of staphylococcal bacteria such as staphylococcus sciuri (Wu et al., 2001). Currently seven different types (I – VII) of SCCmec have been discovered. Each type produces different resistance patterns and characteristics of isolates. For example, types II and III cause resistance to multiple drug classes, while the rest only cause resistance to β-lactam antibiotics. Figure 2.4 depicts the cellular structure and components of MRSA.
2.3.3 Clonal variants

Over time MRSA has evolved to include many different types of clonal variants. Each clone is genetically different, but still maintains the general make up of a MRSA isolate. Several studies have looked into the beginnings of clonal variants, but its origins are still not entirely known (Enright et al., 2002). Currently 2 theories exist to the origins of MRSA clones. The first, proposed by Kreiswirth et al., believes that all MRSA clones are descended from a common SA strain (Kreiswirth et al., 1993). The second theory, brought forth by Musser and colleagues, believes that as a consequence of horizontal transfer and recombination of the mecA methicillin-sensitive precursor cells, divergent clonal lineages have occurred (Musser et al., 1992). Thus, this theory postulates that a
single parent of MRSA is not the origin. Enright et al., in a study typing 359 MRSA isolates collected from 20 countries identified eleven major MRSA clones within five groups of related genotypes. They then compared these to 553 methicillin sensitive isolates and were able to establish the probable evolutionary origins of each of the major MRSA clones (Enright et al., 2002).

Several molecular typing methods have been developed to examine and understand the genetic relationship between clones. These include pulse-field gel electrophoresis (PFGE), multilocus sequence typing (MLST), spa typing and repetitive extragenic palindromic sequence polymerase chain reaction (rep-PCR) testing.

PFGE is considered the gold standard for typing methods because of its discriminative properties (Enright et al., 2002). Analysis occurs by releasing a restriction enzyme, which digests the bacterial DNA, thereby causing the DNA to fragment into several large segments. These segments are then separated by an agarose gel in an electric field with alternating voltage gradients (electrophoresis). This results in banding patterns. The banding patterns of two isolates are compared to each other. If two isolates are of the same clone, then the sites on which the restriction enzyme works and the length of the DNA fragments will be the same. Visually the banding patterns would be identical (Fey, ND). A limitation to the use of PFGE testing is that it is labor intensive, time consuming, and lacks inter-center reproducibility (Nada et al., 1996).

MLST is based on the method of measuring the DNA sequence variations in a set of genes, also known as housekeeping genes, which are required for the maintenance of basic cellular function. The housekeeping genes used in MRSA analyses include arcC, aroE, glpF, gmk, pta, tpi, and yqiL (Berglund et al., 2005). The method involves
polymerase-chain reaction (PCR) amplification followed by DNA sequencing. “A specific allele is assigned to each of the different housekeeping genes,” resulting in an allelic profile for each clone (Deurenberg and Stobberingh, 2008). If five of the seven housekeeping genes are identically sequenced then the isolates are clustered together as genetic clones. The benefit to using MLST typing is that it has a clear standardized scientific protocol that can be adopted across labs; thus the test results are valid and reliable. However, the MLST test is expensive and due to sequence conservation in housekeeping genes does not have the same discriminatory power as PFGE. Nonetheless, it still has proven to be an excellent method to study the molecular evolution of MRSA (Deurenberg and Stobberingh, 2008).

Spa typing compares the length and sequence of a specific repeated DNA element within the protein A gene (spa) from MRSA isolates and determines the sequence variation. Variations can be due to point mutations, deletions, and duplications of spa repeats. In terms of discriminative power, it is half way in between MLST and PFGE testing (Deurenberg and Stobberingh, 2008). The benefit to using spa typing is that it is cheaper, less work intensive, quicker to use and more compatible for building relational databases than MLST (Shopin et al., 2001). Another advantage is the availability of electronic references of spa typing from labs worldwide so a researcher may compare their isolates to a reference database. However the downside to using spa typing is the existence of two different spa classification systems, thus making it difficult sometimes for comparisons (Deurenberg and Stobberingh, 2008).

Rep-PCR is based on the fact that most bacterial organisms contain repetitive DNA sequences that are interspersed throughout the bacterial genome. Specific primers
are then utilized to bind to several of these repetitive sequences. These fragments are then amplified and separated by using agarose gel electrophoresis. The fragments are analyzed using software that overlay the fragments onto each other looking for similarities, by creating dendograms for visually looking at similar bands, by grouping of genetically similar isolates, and comparison to known clonal variants via genetic databases. Genetically related isolates will cluster together by means of having similar sequence patterns. An important advantage of rep-PCR compared to all other molecular techniques is that it is quicker with results within 24 hours, less labor intensive, and often cheaper (Healy et al., 2005).

2.3.4 Classification of MRSA

MRSA can be categorized into three general categories based on its location of transmission and associated risk factors. These includes hospital acquired (HA-MRSA), hospital acquired community onset (HACO-MRSA), and community associated (CA-MRSA). Each of these types has distinct genetic features and plays a different role in the emerging MRSA epidemic (Mostofsky et al., 2011).

HA-MRSA was the first type of MRSA that was isolated. These are the isolates that were originally discovered in 1961, and were the source of the initial and majority of outbreaks that have occurred since (Chambers, 2001). Due to its long standing resilience in hospitals, HA-MRSA has been the popular focus of treatment and prevention strategies. The US Center for Disease Control and Prevention (CDC) defines HA-MRSA as a positive MRSA culture obtained greater than 48 hours after hospital admission, with or without healthcare-associated risk factors (Chau et al., 2011). Associated risk factors include a history of MRSA infections or colonization, and without a history in the past
year of hospitalization, admission to a nursing facility, dialysis, surgery, or of permanent indwelling catheters or medical devices that pass through the skin and into the body (Kaiser et al., 2011). HA-MRSA is generally associated with PFGE type USA100 (Siegel et al., 2006) and SCCmec types I, II, and III (Bukharie, 2010). Klevens et al. in their study examining active, population-based surveillance for invasive MRSA in 9 participating sites found that 85% of all MRSA cases in 2005 were attributed to healthcare onset, 25% of those being HA-MRSA. They also noted that HA-MRSA cases accounted for 64% of all SA infections in U.S. intensive care units in 2003 (Klevens et al., 2007). Numerous other studies have been done, highlighting the fact that the majority of MRSA cases are caused by healthcare associated infections. However, due to aggressive management techniques, education and prevention strategies, the number of HA-MRSA cases is on the decline. Geuilbeua and colleagues in a four year surveillance study from 2005-2008 using MRSA data from the CDC’s Active Bacterial Core surveillance system found that the incidence rate of HA-MRSA infections decreased 9.4% per year in the U.S. population (Guilbeau, 2011). This follows a similar trend in other countries such as England (Pearson et al., 2009).

Healthcare-associated Community Onset (HACO) is defined as a positive MRSA culture obtained less than or equal to 48 hours after admission with identified healthcare-associated risk factors. These include patients who are coming from the community but have recently had a healthcare facility admission, or a history of MRSA infections or colonization. They may also have had recent dialysis, surgery, or a medical device that passes through the skin and into the body such as a catheter. Klevens et al. in their previously mentioned study found that 60% of all MRSA cases in 2005 were attributed
to HACO type of cases (Kleven et al., 2007). The majority of these cases are from individuals who come from nursing facilities or who have some kind of indwelling catheter. HACO-MRSA isolates genotypically match HA-MRSA with the majority of them being USA100 (Limbago et al., 2009).

The first episodes and major outbreaks of MRSA occurred in the hospital setting, and for years it was thought that MRSA was solely a hospital acquired infection. In fact, the majority of policies and prevention strategies crafted over the last 50 years have largely been focused on HA-MRSA and HACO-MRSA and their transmission within a healthcare setting. However in recent years genetically distinct isolates of MRSA have been discovered within communities and individuals who have not had any recent healthcare exposures, leading to the discovery and classification of CA-MRSA. It is estimated that roughly 14% of all MRSA cases are CA-MRSA (IHI, 2008). Currently, there is no one universally accepted definition of CA-MRSA, however the CDC defines CA-MRSA as “the diagnosis of MRSA in an outpatient setting or by a MRSA positive culture obtained \( \leq 48 \) hours after hospital admission in patients without a history of MRSA infections or colonization, and without a history in the past year of hospitalization, admission to a nursing facility, dialysis, surgery, or of permanent indwelling catheters or medical devices that pass through the skin and into the body” (Chua et al., 2011). Other institutions have used the time frame of 72 hours instead of 48 hours (Maltezou and Giamarelou, 2006). In contrast to HA-MRSA, transmission patterns and risk factors for CA-MRSA infections are not entirely understood (Pan et al., 2005). The CDC has described five overarching factors that increase the risk of CA-MRSA transmission. These are known as the five C’s and include crowded conditions, frequent
skin-to-skin contact, compromised skin such as cuts or abrasions, contaminated items and surfaces like towels and toilet seats, and lack of cleanliness specifically hand washing (CDC, ND). Other specific risk factors may include recurrent skin and soft tissue infections (O'Leary et al., 2011). Research has also found that the CA-MRSA isolates are typically PFGE types USA300 and USA400 and also are of SCCmec type IV (Siegel et al., 2006).

CA-MRSA are for the most part skin and soft tissue infections, but do have the potential to present as several severe invasive diseases such as necrotizing pneumonia and fasciitis, as well as osteomyelitis (Adem et al., 2005). The ability of CA-MRSA to cause such severe diseases is in part due to the presence of several different and potent toxins when compared to HA-MRSA. Baba et al. in their analysis of the entire genome of the prototype CA-MRSA strain known as MW2, found that the isolate contained 19 different virulence genes that were not present in HA-MRSA isolates (Baba et al., 2000). A couple of these genes were the Panton-Valentine leucocidin (PVL) genes lukf-PV and lukS-PV. These genes encode for PVL. PVL is a member of the synergohymenotropic toxin family, which is specific to SA and induces pores, via the creation of a heteropolymer, in the membranes of cells (Bradley, 2006). PVL is a dermonecrotic toxin and has been directly linked to causing necrotizing pneumonia and fasciitis.

The incidence of CA-MRSA has been on the rise in recent years, and has been the source of several outbreaks within communities as well as within hospitals. However, its true prevalence in the community is not known, nor are its risk factors entirely understood (Gosbell, 2005).
2.3.5 Economic burden

It is estimated that each year approximately two million patients in the US contract a hospital acquired infection, and that of these 90,000 actually die (APIC, 2010). The CDC estimates that annually there are 94,000 invasive MRSA infections in the U.S. population. The majority of these cases (75%) were uncomplicated bacteremias, however overall about 19,000 or 18% died during their initial hospitalization. The CDC also estimates the standardized incidence rate of invasive MRSA to be 31.8 per 100,000 U.S. population.

As one can imagine, the economic cost and burden of the treatment and prevention of MRSA is tremendous, continues to grow, and has become a major public health issue (Hebert and Weber, 2011). In 2005, MRSA infections accounted for 368,600 hospital stays. That represents a 10-fold increase since 1995 (IHI, 2008). I.M. Gould in his cost attributable study of MRSA found that MRSA costs exceed methicillin susceptible Staphylococcus aureus (MSSA) treatment cost by $3700 for mixed group infections, $6900 for bacteremias, and up to $10,000 for intensive care unit stays (Gould, 2006). Rojas et al., in a cost study, concluded that MRSA adds 1.5 to 4.2 billion dollars in hospitals cost annually with direct medical costs of up to $35,000 per patient (Rojas and Liu, 2005). One element of the additional cost is the increased length of stay which is often two - three times longer than non MRSA infected patients and double those of MSSA (Graffunder and Venezia, 2002). Often the burden of payment falls not on the individual but on society in the form of increased taxes due to increased use of government resources and programs as well as from increased insurance premiums. This cost to society has been estimated to range from 17 billion to 30 billion dollars (Gould
2006). It is important to note, that even though there is an increased cost from surveillance and elimination programs, this is frequently offset by a cost savings of approximately 2.9 million dollars. This cost savings is chiefly due to faster turnover of a hospital bed. Thus these treatment and elimination programs even though costly have proven to be a key in the battle against MRSA.

2.3.6 Treatment

In January, 2011, the Infectious Disease Society of America (IDSA) released a detailed treatment guideline for MRSA. They stated that the treatment and management of MRSA is based on two key principles; identification and elimination of the organism (Liu et al., 2011). The method of elimination depends on the location and type of infection and can either be antibiotic therapy or surgery (Kumar and Clark, 1998, p.106). In the management of skin and soft-tissue infections (SSTIs) with community-associated MRSA, the primary treatment for cutaneous abscesses is incision and drainage without the use of antibiotics. Antibiotic therapy is only recommend for abscesses associated with severe or extensive disease such as those involving multiple sites of infection, when there are signs and symptoms of systemic illness, and when the abscess is in an area difficult to drain such as the face, hands, and genitalia. Antibiotic therapy is also recommended for outpatients with purulent cellulitis. Empirical antibiotic therapy for community-associated MRSA includes clindamycin, trimethoprim-sulfamethoxazole, tetracycline, and linezolid. For patients who are hospitalized with complicated skin and soft tissues infections such as those with deep abscess or surgical wound infections the primary treatment is debridement of the area and empirical antibiotics which may include vancomycin, linezolid, daptomycin, and clindamycin (Deresiewicz et al., 2005).
Decolonization with the use of mupiricin and/or chlorhexidine is an option for patients who have recurring MRSA infections, but should not be used in active disease (Ridenour et al., 2007). Other measures such as maintaining good personal hygiene with regular bathing and hand washing with soap and water or an alcohol-based hand gel, should be used also be used as a general rule (Korczak et al., 2010).

2.3.7 Prevention

The development and implementation of prevention strategies for MDROs, and specifically for MRSA, has been an ongoing initiative ever since the first resistant isolates were discovered (Vermont Program for Quality in Health Care, INC. ND). Over the years the focus has gone from reduction to complete elimination (Duerden, 2009). Professional organizations and key stakeholders such as the Association of Professionals in Infection Control (APIC), Society for Healthcare Epidemiology of America (SHEA), the Institute for Healthcare Improvement (IHI), the U.S. government’s Healthcare Infection Control Practices Advisory Committee (HICPAC), and the CDC have all initiated projects, campaigns, and resources either separately or jointly to combat MRSA (Smith et al., 2008). In fact, the CDC has declared the prevention of hospital acquired infection including MRSA to be one of its five winnable battles and therefore one of its top priorities (CDC, ND).

Prevention strategies focus on three main areas: 1) risk assessment and surveillance; 2) education and policy change; and 3) stewardship and decolonization strategies. The latter strategies are those that target zero tolerance and total elimination (APIC, 2010).
The purpose of risk assessment is to get an understanding of the problem at hand. According to APIC, hospital specific MRSA risk assessment will result in the baseline description of hospital MRSA incidence, prevalence, transmission patterns and will help identify populations that are more likely to be colonized (APIC, 2010). Information derived from the risk assessment will drive the improvement and prevention process. Retrospective as well as prospective surveillance data is key and the core essence of risk assessment data. This will indicate the trend in which the infection rate is moving towards, and be the foundations on which goals, interventions, and evaluations are based on (APIC, 2010). Surveillance can be active or passive. Active surveillance is defined as “actively” seeking out patients who may have a specific condition (Muto et al., 2003). This is opposed to simply waiting for notification that a patient has a specific condition i.e. passive surveillance. The IHI has noted the benefit of active surveillance in their MRSA prevention guide titled “5 Million Lives Campaign. Getting Started Kit: Reduce Methicillin-Resistant Staphylococcus aureus (MRSA) Infection How-to Guide” (IHI, 2008). Several hospitals across the country have successfully implemented active surveillance for MRSA of all admissions to their respected hospitals (BD, 2011). Successful surveillance is based on having a clear, concise, and constant surveillance definition in place and following sound principles of epidemiology and statistics (APIC, 2010). Findings from risk assessment should be communicated to key stakeholders and leaders, and translated into educational material and opportunities as well as into policy changes.

Educating patients, healthcare workers, and the general public is an integral part of MRSA prevention. In fact education has been an important part of infection control
programs for decades (Clark, 2006) and has been proven to reduce infection rates dramatically (CDC, 2002). Haley et al. noted that hospitals with good educational infection control programs could reduce infections by 32% (Haley et al., 1985). Educational programs must be based on the needs of the population and goals need to be clear, directly communicated to learners, emphasized often, and promoted in appropriate skill levels. There are different levels and methods of learning (APIC, 2010). It is important to understand and assess beforehand which level or method is most appropriate for the institution at hand. This will lead to better understanding, effective change, and ultimately to decreased transmission of MRSA.

It has been well established that the chief mode of transmission of MRSA from one person to another (patient to patient, patient to healthcare worker, and vice versa) is by environmental contamination, specifically of the hands. Proper hand hygiene can reduce MRSA by 50% (Lederer, 2009). Hand hygiene etiquette among health care workers is poor, with the average U.S. hospital compliance being less than 50% and far lower in intensive care units (McGuckin et al., 2009). APIC suggests that a comprehensive educational and proper hand hygiene program be set up in each hospital (APIC, 2010). The CDC recommends the following nine guidelines for an effective hand hygiene program (Boyce and Pittet, 2002):

1. Program should be multidisciplinary and at all levels of healthcare from visitors to physicians

2. Hand washing should be done with soap and water if hands are visually soiled

3. Alcohol hand rub should be used for non-soiled hands, except for in the case of c. difficile where soap and water should be used
4. Wash hands before and after patient contact

5. Hand washing should occur before and after contact with a patient’s environment

6. Hands should be protected with gloves, but washed prior to wearing gloves

7. Provide educational materials to all levels of healthcare

8. Conduct regular hand hygiene audits

9. And hold all persons (physicians, nurses, staff and visitors) accountable for hand hygiene practices

Several studies have proven that by merely correctly conducting hand hygiene, rates of infections have decreased. In one such study by Song et al., the authors sought to measure the impacts of hand hygiene compliance in a neonatal ICU by conducting monthly hand hygiene compliance audits before or after patient contact (Song et al., 2011). They observed that proper hand hygiene compliance resulted in a 40% reduction of MRSA transmission, which translated into an avoidance of 79.4 extra days in the hospital and $215,000 per infected patient.

Contact precautions also play an important role in minimizing the transmission of MRSA from one person to another (APIC, 2010). Contact precautions consist of gloves, gowns, masks or face shields, policies delineating proper cleaning and disposal of soiled or contaminated environment (Muto et al., 2003). Patients should be placed in contact precautions and isolation as soon as MRSA is identified. Therefore policies and a proper process must already be in place for isolation and contact precautions. APIC highlights
the following strategies to successfully implement contact precautions and subsequently reduce MRSA transmission (APIC, 2010):

1. Implement an alert system to flag patients who are MRSA positive immediately after diagnosis so they can be placed into contact isolation and precautions.

2. Have a process in place as to when, how, who, and by whom to place someone in contact isolation.

3. Develop a system for identifying patients with MRSA who are being transferred from within and outside the hospital.

4. Have a method to measure adherence to contact isolation and precaution policies.

Risk assessments and education programs will allow for an understanding of what practices are being followed, what processes are working and not working, where standards lack, and the overall infection trend. All of these aspects when evaluated will need to be translated into policy changes. Policy change is not easy to do, as many institutions and professions have their own subculture that may resist change (Grant, 2011). Policy change is often based on the larger organizational cultural change, which can be complex and difficult to achieve (Scott et al., 2003). It is often described as being fluid, unpredictable, filled with obstacles, and requires commitment, time and flexibility (Kimball, 2005). Culture change can either be first or second order (Langfield-Smith, 1995). First order culture change is simply “doing what you are doing, but better” (Deal, 1982), while second order culture change is effectively creating an entirely new way of thinking (Bate, 1999). Successful cultural change is ideally based on three elements. These include: support and commitment of leadership, shared vision and values among
all stakeholders, and involvement and ownership at all levels (Kimball, 2005). In “Making the Journey to Cultural Change in Healthcare,” a white paper authored for GE Health, Anita Young describes the four steps to achieving effective cultural and policy change (Young, 2000). These include:

1. Obtaining knowledge and being aware by realistically understanding the current culture, the current data trends, and having a vision of what needs to change and how to achieve it.

2. Demonstrating and encouraging the desired behaviors and outcomes while determining the decision making process.

3. Communicating to all levels of the organization as to how and what is going to change. These messages should be constant and open for discussion with ongoing dialogue.

4. Aligning top leadership and performance management with the organization’s core values and issues, with an understanding of the needed competencies. This is achieved by linking behaviors and goals to recognition and compensation.

To achieve these goals it is also important that one has a champion from among the organization to tout the importance of cultural change, and that that the champion is constantly grooming additional champions.

The third and final level of MRSA prevention strategies focuses on environmental cleaning, decolonization, and antimicrobial stewardship. MRSA is a very hearty organism and has the ability to survive in the environment, sometimes up to 56 days after
contamination (Huang, 2006). Contaminated surfaces become a reservoir for patients or healthcare workers to transmit or acquire MRSA (APIC, 2010). In a study examining the reduction of MRSA by enhanced and detailed environmental cleaning, Datta and colleagues found that thoroughly cleaned rooms significantly decreased the chances for transmission of MRSA to other occupants (Datta et al., 2011). It is essential that all members of the staff, both environmental services and clinical, are properly educated regarding the importance of thorough cleaning and decontamination and the use of appropriate cleaning procedures (IHI, 2008). It is also very important to have clear policies and understanding of who is cleaning what surfaces in each room. Random regular audits of environmental cleaning and cleaners should also be conducted with feedback to the room cleaners provided (APIC, 2010).

In those patients who are colonized with MRSA and may be transmitting it to others in their own personal environment it may be necessary to decolonize them. Decolonization is recommended in specific circumstances and should not be done routinely on a patient. Decolonization strategies include mupirocin nasal ointment which is to be swabbed in the nasal passage, and washing the body in affected areas with chlorhexidine (Bell, 2007). Often there is no need for coinciding systemic antibiotic treatment (APIC, 2010). Short term goals of decolonization include interrupting the transmission or MRSA, eliminating MRSA carriage, and reducing the risk of infection in high risk groups such as intensive care patients. Decolonization has been recommended preoperatively in certain populations like cardiac surgery patients to avoid the chances of surgical site infections (Anderson et al., 2008). There is a mix of results in terms of the efficiency of decolonization. In one study by Dow and colleagues, the authors found that
decolonization of patients resulted in a lower MRSA infection rate in a group of patients when compared to those who were not decolonized (Dow et al., 2010). The authors concluded that MRSA decolonization can be successful in treating hospitalized patients. However, a study conducted by Lucet and Regnier, concluded that the contribution of MRSA decolonization to cross-transmission limitation is probably small in comparison to the impact of precautions (Lucet and Regnier, 2010).

Over the years there has been unnecessary use, misuse, overuse and abuse of antibiotics. It has been proposed that these factors have contributed to antibiotic resistance (Malhotra-Kumar et al., 2007). A crucial strategy in the prevention and control of antibiotic resistance is managing and guiding the principles of antibiotic prescribing. This strategy is known as antimicrobial stewardship. It is a program set up by hospitals to guide clinicians in using the correct antibiotics, doses and length of treatment. Antimicrobial stewardship strategies result in the following (APIC Guideline 2010):

1. Reduced resistance

2. Utilization of local antibiogram data and antibiotic susceptibilities

3. Decreased incidence of infection

4. Use of appropriate evidence based treatment guidelines and

5. Improved clinical outcomes and patient safety

The role of a stewardship program is to establish communication of guidelines within all levels of patient care providers, identify MDRO transmission patterns, and develop policies to stop the transmission. Antimicrobial stewardship programs have proven
effective in reducing infection rates, resistance rates, and costs from both antibiotic use and patient turn over (Goff, 2011).

2.4. Medical Informatics

2.4.1 Introduction

It has been a little over a decade since the Institute of Medicine (IOM) published its detailed report *To Err Is To Be Human: Building a Safer Health System* (Institute of Medicine, 2000) in which they highlighted the significance and concerns related to the status of medical errors. The IOM estimated that up to 98,000 deaths occur each year from medical errors and most, if not all of these were avoidable and due to a breakdown in systematic processes. They developed and recommend a four tiered approach, as a standard for improvement, to achieve a better patient safety record. This four tiered approach included the following steps:

1. Establish a national focus to create leadership, research, tools, and protocols to enhance the knowledge base about safety.

2. Identify and learn from errors by developing a nationwide public mandatory reporting system and encourage health care organizations and practitioners to develop and participate in voluntary reporting systems.

3. Raise performance standards and expectations for improvements in safety through the actions of oversight organizations, professional groups, and group purchasers of health care.
4. Implement safety systems in health care organizations to ensure safe practices at the delivery level.

Leape and Berwick in their article examining what progress has been achieved 5 years after the initial IOM report, acknowledge that even though all four tiers have not been implemented the topic of patient safety has been moved to the forefront of all agendas, public and private (Leape and Berwick, 2005). They note that one important result from the report is that organizations such as the Agency for Healthcare Research and Quality (AHRQ), National Institute of Health (NIH) and the CDC have all allocated tremendous amounts of funding for the development and of new technologies to reduce medical errors (Leape and Berwick, 2005). This new national forum will also sanction novel transitional research and create opportunities for faster implementation to the bedside (President’s Council of Advisors of Science and Technology, 2010). Leape and Berwick also note that the field of medical informatics and specifically the advent and implementation of electronic health records facilitates the goal of reducing medical errors and enhancing patient safety.

2.4.2 Definition

William Hersh, in his article entitled Medical Informatics: Improving Health Care Through Information, states that the healthcare field is an information based science since the essence of clinical practice involves gathering, synthesizing, and acting on information (Hersh, 2002). However, he also states that there is a rising concern that information is not being used as effectively as possible in healthcare. One method of increasing the effectiveness and use of information in the healthcare field is by investing
in and utilizing the resources and ideas of the genre of medical informatics. Edward
Shortliffe, in his book entitled *Biomedical Informatics: Computer Application in
Healthcare and Biomedicine* (Shortliffe, 2006), defines medical informatics as the
application of information technology to the healthcare industry. This definition is meant
to be broad. Medical informatics has an extremely wide use and scope and includes
decision support systems, information/knowledge retrieval systems, imaging and
telemedicine systems, support of medical education, standards of interoperability, patient
and public health information surveillance systems, electronic health records and
electronic information exchanges.

The field of medical informatics essentially began with the invention of computers
and their integration in the use of clinical practice. The original focus of the field was to
automate and streamline complicated medical processes. Over the years, medical
informatics has developed into a robust and complex field that is focused not only on
removing medical errors but also on the integration of electronically captured and
exchangeable data. However, due to the sensitivity and nature of the data being collected
i.e. patient personal health data, the healthcare industry lags behind many other fields
such as banking in full utilization of information technology to effectively and efficiently
automate process (Shortliffe, 2006). Medical informatics is based on several core themes.
These include: standards, terminology, usability, and demonstrated value (Hersh, 2002).
Standardization is vital because this allows for the common understanding and interface
among multiple users across various systems (McDonald, 1997). Standards include
communal methods for data collection, standard clinical guidelines to ensure the integrity
of data collected and that it is of the same value across institutions, collective
mechanisms for communication to allow the transfer of data from one facility to another, and system messaging standards such as HL7 to again ensure the intra and inter-facility flow of data. Terminology across institutions and industries also needs to be standardized thus guaranteeing that data and results are measured and reported consistently (Powell K, ND). The tools and resources developed and utilized in medical informatics also need to be able to work across facilities. William Hersh relates that it is necessary that systems be integrated into technical work flow and demonstrate other benefits, specifically when they require more time or effort in the part of the user (Hersh, 2002). This means that new systems and technology need to be able to work smoothly in conjunction with existing systems. Lastly, research, discoveries, and new technology in medical informatics must be needed and have a value to the healthcare industry (Powell K, ND).

2.4.3 History

The beginnings of medical informatics start in the late 19th century, 55 years before the first electronic digital computer was built, when Drs. Billings and Hollerith invented a punch card based tabulating machine. The punch card system was first used in 1890, to process U.S. Census data (Becker, 2006). These punch cards had 288 slots for data. Due to this invention they were able to process the census data of 62 million Americans in a 30 day time period. The punch card machines were the prototypes for computers. With the advent of computers in 1946, medical researchers began to look into its use for the progression of the medical sciences (Collen, 1995). As computer languages were developed in the 1960’s, researchers began to develop basic hospital information systems in the 1970s. The first system was built and deployed in 1971, at Massachusetts General and was known as Computer Stored Ambulatory Record System or COSTAR.
COSTAR, which is still in use today, primarily collected billing, admission, discharge and lab data for patients (Rabbani et al., 1998). It was around this time in which the term medical informatics began to appear (Collen, 1995). As systems were developed further and “became more integrated instead of modular” usage for direct patient care increased (Shortliffe, 2006). By the end of 1980’s 80% of physicians had a computer in their offices (Becker, 2006). The 1990’s saw an era where computers were the standard for patient care as well as hospital quality control and management.

At the beginning of the 21st century the IOM published its To Err Is To Be Human: Building a Safer Health System report and thus pushed medical informatics to the forefront of predicative, preventative, personalized, and participatory medicine. In 2004, President George W. Bush issued Executive Order 13335, which detailed the creation of a National Health Information Technology Coordinator and incentives to hospitals for the adoption and use of health information technology (Bush, 2004). This was reiterated by President Barak Obama in 2009, when federal money was made available via the American Recovery and Reinvestment Act (ARRA) for research as well as additional incentives to facilities for the adoption and use of health information technology including electronic health records (US Congress, 2009). Today medical informatics is the key to patient safety and the future of medicine.

2.4.4 Impact and use

Medical informatics is a fundamental component to improving the quality of healthcare (Weissman and Hasnain-Wynia, 2011) as it deals with all aspects of understanding and promoting the effective organization, analysis, management, and use of information in healthcare (AHRQ, 2002). It seeks to transform an error prone,
inefficient, traditional paper based manual system into a streamlined, effective and proficient process. In recent years, outstanding novel research has been conducted and practical measures implemented that have changed the workflow of clinical practice. One of the agencies helping to move things ahead is the Agency for Healthcare Research and Quality (AHRQ). Over the past 30 years they have funded numerous informatics studies trying to improve patient safety as well as some looking to advance the sharing of electronic data. Some of their patient funded patient safety research includes projects that “examine the acceptance of, benefits of, and barriers to the use of stand-alone, handheld decision support systems (DSSs) in an ambulatory setting to improve prescribing patterns in order to prevent medication errors”, “develop an infrastructure to support automated surveillance of errors by using a natural language processor called MedLEE to code the information contained in patients' electronic health records to detect and characterize medical errors”. They have also helped develop a computerized national chronic disease databank system and a “computerized infectious disease monitor to minimize the inappropriate use of prophylactic antibiotics, optimize the use of therapeutic antibiotics, and detect the presence of nosocomial infections” (AHRQ, 2002). These grants and projects have greatly impacted the field of medical informatics. In a study by Kho et al., using current IT infrastructure, the authors created a citywide electronic notification system to prospectively track and share information regarding all known patients with MRSA. With this system in place they are able to track 17,000 patients with a history of MRSA infection or colonization across the Indianapolis region. Whenever a known MRSA patient comes into any of the regions hospitals, the admitting clinician is alerted to the patients’ MRSA status, thus prompting the patient to be placed in isolation (Kho et
al., 2008). This system greatly improves patient safety and the quality of healthcare, by ensuring that prompt notification about MRSA status occurs and that proper and isolation policies and procedures are enacted.

2.4.5 Electronic health records

The medical record is a collection of all the data acquired and created during a patient’s course through the healthcare system (Shorliffe, 2006). Its purpose is to recall observations, inform others, to instruct students, to gain knowledge, to monitor performance, and to justify interventions (Reiser, 1991). It includes patient information such as demographics and diagnoses, physician and nursing notes, labs results, and other information related to the health of a patient. The overarching goal of the medical record is to advance the application of health sciences by methods that improve the well-being of patients, including the conduct of research and public health activities which address population health (Shorliffe, 2006). Traditionally this process and record have been paper based (AHRQ, 2002). The paper based medical record is currently used by approximately 80% of physicians (President’s Council of Advisors of Science and Technology, 2010), and has several limitations. First of all, because it is a single paper based copy it is accessible to only one person at a time (Shorliffe, 2006). The treatment and care of a patient is based on the integration of many different clinical skills from pharmacists to nurses to physicians. The medical record may also be incoherent or illegible based on poor organization or bad hand writing. It is entirely possible that some information is missing, such as laboratory results, or loose papers have been lost (Tufo and Speidel, 1971). Patients will potentially have multiple medical records if they visit more than one healthcare provider. Often these records are not shared between the multiple healthcare
Another key limitation to paper based medical records is that they lack standards of the type, quality, and quantity of data collected. Maintaining these paper based records is also an issue as they take up space and need to be stored in secure fireproof locations. These resources may not be available and will add costs to medical facilities. Lastly, data can only be manipulated mentally or on paper to take relative clinical information away (Shorliffe, 2006).

The understanding of the issues and limitations of paper based medical records led the United States government to highlight the need to move to an electronic based system. President George W. Bush in his 2004 State of the Union address acknowledged the benefits of using an electronic system and urged all health care providers to switch by 2014. Funding in 2005 was doubled to 100 million dollars and 125 million in the 2006 federal budget (Flether, 2005). President Obama reiterated this call by adding in economic incentives to those who switched early on (US Congress, 2005) and penalties to those who did not switch over by 2015 (Pear, 2010).

Edward Shortliffe defines an electronic health record (EHR) as a repository of electronically maintained information about an individual’s lifetime health status and healthcare, stored such that it can serve multiple legitimate users of the record (Shorliffe, 2006). It is the electronic version of the patient’s medical record that automates and streamlines the clinician’s workflow by being integrated with a health system’s other valuable systems such as laboratory and decision support. An electronic medical or personal record is the patient’s legal record that they can take from one place to another (Archer, 2011). The electronic medical record is the source of data for an electronic health record and must be established prior to the EHR (Garets and Davis, 2006).
EHRs have the ability to reduce medical errors by improving the accuracy and clarity of recorded clinical and non-clinical data (CMS, 2011). In a study conducted by Gearing et al., they found that an EHR system can reduce vital sign documentation errors by half to an error rate of 5% when compared to the manual documentation process (Gearing et al., 2006). Deckelbaum et al. conducted a study to examine whether implementation of an EHR could be used to improve attending involvement in daily care, enhance surgical revenue, and lower mortality of trauma patients. They noted that with the implementation of an EHR, attending surgeon documentation notes and divisional annual revenue increased while there was a significant reduction in hospital mortality (Deckelbaum et al., 2009).

EHRs also have the potential to improve the quality of health care. They do this by their integration with other clinical software such as decision support systems (DSS). Decision support provides narrative information requiring further processing and analysis by providers before clinical decisions are made (Pearson et al., 2009). They use current best practices to steer physicians into making the best clinical decision. Current best practices and clinical guidelines are imbedded in and interfaced with DSS. They are triggered when a clinician needs to make a decision regarding the care of a patient. For example, when a clinician is ordering a specific antibiotic for a patient the DSS will prompt specific queries about the patient and guide the clinician to best practices and clinical guidelines. In a study examining the use and benefits of DSS in a hospital intensive care unit (ICU) with mainly severe sepsis patients, researchers concluded that following the implementation of DSS the adherence to best practices and clinical standards increased significantly by 35%. They also witnessed improved diagnostics,
increase in antibiotic-free days and a shortened time until antibiotics were administered (Tafelski et al., 2010).

Even though EHRs have tremendous potential and are the way forward, there are several limitations and disadvantages to their implementation. The first disadvantage is the initial cost. Transforming a paper-based system into an automated integrated computer system requires an investment of time, money, and manpower. Dick et al., in their book *The Computer-Based Patient Record: An Essential Technology for Health Care* states that allocating capital to information systems is still a challenge, specifically at a time when healthcare organizations need to reduce their costs (Dick et al. 1997). It is estimated that startup costs for EHRs are approximately $32,000 per physician and roughly $1200 maintenance costs per physician (National Committee for Quality Health Care. 2006). Often the return on investment takes several years to attain. Large hospitals usually within 3 years will achieve a net savings of 5-10 million dollars and a reduction of medical errors by 55%. However, for smaller and rural hospitals the return on investment may take much longer (California Legislative Analyst Office, 2007). Another disadvantage is that EHRs require time to learn. Many healthcare workers may not have the time to effectively learn a new system. In fact many healthcare workers may not feel the need to learn a new system or may even feel apprehensive about changing their methods (Shorliffe, 2006). Confidentiality and security issues are associated with who has what level of access and is also a deterrent to adopting an EHR. Policies and work flows will need to be adjusted and changed accordingly (Lori Gurley, 2004). This may prove difficult for some of the larger hospitals who have complex, and often competing, bureaucracies. Another disadvantage of EHR implementation is the lack of a standard
terminology, system architecture, and indexing. In order for data to be shared, proper interfaces must be available linking different systems to each other. The adoption of a standard architecture and language is something the federal government is working on (Young K, 2000).

Despite its benefits, incentives, and success stories from some early adopters, the current level of those adopting EHRs is limited. It is estimated that in 2009, 46% of U.S. office based physicians used some kind of EHR system. Among these, currently only 9% have a complete operational EHR (National Center for Health Statistics, 2005). It is important to note though, that the rate of EHR adoption has greatly increased in the past decade. The rate has gone from 18% in 2001, to 25% in 2005 and then to 46% in 2009. This rate is expected to dramatically increase until 2015 when EHRs are mandated.

2.4.6 Health Information Exchange and Regional Health Information Organizations

The fundamental concept of EHRs is essentially the aggregation and exchange of data related to a patients’ health. In regards to EHRs this data is exchanged within a health system to all those concerned with the patients care and also to those responsible for administrative duties like billing, admission and discharge. A goal of medical informatics and the implementation of EHRs is to go beyond the single treating hospital and allow data to be exchanged between institutions on a continuous and systematic basis. This concept is known as a health information exchange (HIE). In a 2008 report to the Office of the National Coordinator for Health Information Technology, the National Alliance for Health Information Technology (NAHIT) defined health information exchanges as the electronic movement of health-related information among organizations according to nationally recognized standards and policies (HIMSS, 2009). HIEs are
essentially EHR models applied on a grander scale across multiple independent institutions (HIMSS, 2009). The goal of a HIE is to facilitate access to and retrieval of clinical data to provide safer, more timely, efficient, effective, equitable, patient centered care (Weniger, 2006). It is important to note that HIEs have a multidirectional flow of data between providers and other key stake holders such as consumers, employers, and government (HIMSS, 2009).

HIEs have several benefits to key stake holders. For patients, HIEs allow patients to have control of their health record. It also potentially avoids duplicate testing and unnecessary procedures, while improves the doctor patient relationship. For providers HIEs improve outcomes and save money by enhanced communications, streamlined workflow, reduced duplicate testing, and easier access and retrieval of clinical data. For employers HIEs decrease healthcare costs by helping employees take charge of their medical care and give them increased access to high quality medical professionals. Lastly, for communities it reduces chances of lost or unavailable records, and encourages coordination and collaboration of care which in turn decreases costs. It also promotes transparency and enables community wide public reporting, which is increasingly being mandated by state legislatures (Florida Association of RHIOs, 2009). HIEs also create a mechanism for increased cooperation between research and clinical practice.

In response to President George W. Bush’s 2004 Executive Order detailing the creation of a National Health Information Technology Coordinator, the Department of Health and Human Services (HHS) released their plan for a new informatics based health care system (Thompson and Brailer, 2004). Part of this plan was to lay the foundation for a National Health Information Network (NHIN). The NHIN would be comprised of
multiple regional health information organizations (RHIOs). The Healthcare Information and Management Systems Society (HIMSS) defines RHIOs as a “neutral organization that adheres to a defined governance structure which is composed of and facilitates collaboration among the stakeholders in a given medical trading area, community, or region through secure electronic health information exchange to advance the effective and efficient delivery of healthcare for individuals and communities” (HIMSS, 2009).

The HHS envisioned the federal government playing a key role in supporting and guiding the formation of HIEs and RHIOs. They specifically recognized and addressed the issue of rural hospitals. Acknowledging that health disparities between urban and rural areas exist, they highlighted the need for a rural RHIO, possibly linked to an urban medical center or RHIO. This would reduce variability of care, increase knowledge and education among rural healthcare providers, and decrease the gap between communities (Thompson and Brailer, 2004). The IOM identifies several key initiatives that must be first adopted for rural RHIOs to take hold. These include adopting a rural community focus, developing consistent regulations and payment polices, assist collaborations and demonstrations in rural areas, and ensure high speed internet access to rural communities (IOM, 2005). In a study by Wang and colleagues, the authors compared the internet use among those who, for medical reasons, were limited in their ability to travel from rural and urban communities. They found that a digital divide existed between urban and rural residents (Wang et al., 2011).

In order for HIEs and RHIOs to achieve success there are several leading practices that need to be kept in mind. The first is engaging key stakeholders early on in the development process. Open and regular communication is very important. This will
help develop trust and support among all the key players. Realistic goals must also be set with an approved time line from all stakeholders. Also an evaluation of current and future IT standards and needs must be completed. If health systems are to be sharing data with each other, then the systems must be interfaced. Using national standards such as HL7 messaging and other interoperable systems is the first step in this process. Lastly, listening to the needs of the community in which the RHIO will serve. Getting feedback from future users will allow for greater appreciation and usability (HIMSS, 2010).

Although the technology and incentives for constructing HIEs and RHIOs exist, there are several limitations. The first major limitation to creating a RHIO is the availability of standardized information technology systems across and within healthcare systems. The initial cost of purchasing or developing these systems is high. Smaller community and rural hospitals may not have the startup funds to begin this process. Another related issue is that the multiple existing systems may not be able to interface with each other, and therefore data exchange cannot occur. It is also important to note that potential partners in RHIOs may in actuality be competitors within a community. If this is the case, one organization may not want to give up their competitive edge by joining forces with other regional institutions. Uncertainty about who truly benefits from the RHIO may also cause confusion and a lack of interest. Lastly, a major limitation to regional data sharing stems from data security and privacy issues (Gorssman et al., 2008).

2.4.7 HIPAA, privacy and security

In the past decade there has been an increasing recognition of the role and value of information technology in clinical settings. With the advent of HIEs and RHIOs, national public health databases, and biosurveillance projects the dissemination of patient
health information has become relatively easier and wider spread (Shapiro et al., 2011). However, the transmission of health related information and data raises several legal issues and concerns related to privacy, confidentiality, and data security. In 1996, the United States government passed the Health Insurance Portability and Accountability Act (HIPAA). This act set forth rules for access, authentication, storage and auditing and transmittal of electronic health records (Shortliffe, 2006). Current threats to medical record privacy include administrative actions such as the release, loss, or misclassification of records, access by unrelated parties such as insurance agencies or drug companies (EPIC, ND).

The use of health information technology has been identified as a critical tool for improving health quality, access to healthcare, and empowering consumers. Central to the use and application of health information technology are the concepts of privacy, confidentiality, and security and the assurance that these concepts will be top priorities. These three terms are commonly intertwined and interchangeable, but are distinct in regards to their definitions and applications. Privacy refers to the right of an individual to keep information about themselves from the knowledge of other people, while confidentiality refers to the guarantee that specific information about an individual will not be disclosed without proper consent except as the law allows. Security refers to the mechanisms in place to assure patient information is and remains both private and confidential. Thus privacy relates to an individual whereas confidentiality refers to the organization maintaining the private information, and security refers to the policies and steps that protect both patients and organizations keeping health care data. In the context of health information technology, it entails such issues as to how data is collected, where
it is stored, who has access to the data, and what kind of protective measures are in place to ensure its safety. Federal laws such as HIPAA also play a significant role in defining the three concepts of privacy, confidentiality and security in the context of health information management. Each concept is vital to the integrity of implementing and using health information technology in multiple patient care settings (Shortliffe, 2006).

A key barrier to the implementation of EHRs is the issue of data security and privacy. It is important to have developed policies as to who gets access and at what level do they have access to. Safe guards and mechanisms need to be in place as to how much information is shared and by whom. Computer systems must have secure log-ons that are audited from time to time to keep a system of checks and balances (Shortliffe, 2006).

Even though these issues pose a threat and barrier to the development and wide spread use of EHRs, they should not be taken a deterrent. Current resources and technologies should be used to develop novel strategies and information exchange systems where data can be safely transferred all within the realm of the law.

2.4.8 The use of medical informatics and health information technology in infectious disease research

Medical informatics can be a very crafty research tool (President’s Council of Advisors of Science and Technology, 2010). It allows for multiple levels of information across disciplines to be leveraged in a short period of time. In fact some data feeds can be real time (Eggers et al., 2007). Over the years medical informatics and healthcare technology have been used to generate novel techniques for surveillance and have in general enhanced the quality and breadth of infectious disease research. In a study examining the automated detection and reporting of notifiable diseases using EHRs,
researchers at a Massachusetts hospital found that the EHR based surveillance system discovered a higher percentage of cases and at a quicker rate when compared to traditional passive surveillance techniques (CDC, 2008). Health information technology has also played an innovative role in MRSA research. In a study by Kho et al., the authors used computer generated log-in data and geographical information systems (GIS) software to document and map the contact patterns and transmission of MRSA between healthcare providers and patients. By creating detailed time sequence animations they were able to ascertain specific factors that contribute to the spread of hospital acquired infections such as using the same blood pressure cuff from one patient to another and the lack of proper isolation (Kho et al., 2006).

2.4.9 Chapter 2 Summary

SA, a bacterium discovered in the 1800’s but probably around for centuries, was once treatable by penicillin. However within years of the discovery of penicillin and its wide spread use, SA became resistant to this wonder drug and its replacement methicillin. Within the past 50 years, MRSA has grown from a being single drug resistant organism to be becoming a multi-drug resistant organism. It has genetically evolved over the years from being a predominantly hospital acquired infection to a community associated infection. Community associated infections are defined as the diagnosis of MRSA in an outpatient setting or by a MRSA positive culture obtained less than or equal to 48 hours after hospital admission in patients without a history of MRSA infections or colonization, and without a history in the past year of hospitalization, admission to a nursing facility, dialysis, surgery, or of permanent indwelling catheters or medical devices that pass through the skin and into the body. MRSA has gone from being a few sporadic cases to
epidemic levels and finally to endemic levels. All of this has brought the prevention and treatment of MRSA to be a top priority of public health institutions.

A key component to the prevention and treatment of MRSA is the field of medical informatics. Medical informatics is defined as the application of information technology to the healthcare industry, and includes decision support systems, information/knowledge retrieval systems, imaging and telemedicine systems, support of medical education, standards of interoperability, patient and public health information surveillance systems, electronic health records and electronic information exchanges.

Electronic health records are an evolving concept defined as a systematic collection of electronic health information about individual patients or populations (Gunter and Terry, 2005). They are electronically stored and accessed at a hospital or healthcare providing entity and gather information from a multitude of computer systems including laboratory data, hospital admission and transfer systems, billing data, computerized physician order entry systems, and other relevant clinical data systems. EHRs have several benefits when compared to the traditional paper based system. Some of these benefits include a reduction in medical errors, streamlining of the clinical workflow, easy accessibility among the many different healthcare providers, and a central location for all data. The adoption of EHRs is increasing, but still is limited with only 9% of healthcare providers using a complete EHR system, but with 46% using some kind of system. This number is expected to increase until 2015, when EHR systems will be mandatory as mandated as by federal legislation.
EHR systems lay the groundwork and foundations of electronic HIEs. HIEs are “the electronic movement of health-related information among organizations according to nationally recognized standards and policies.” As described, the goal of a HIE is to “facilitate access to and retrieval of clinical data to provide safer, more timely, efficient, effective, equitable, patient centered care.” Development of HIEs has several benefits to key stakeholders. They allow patients to have control of their health record. It also potentially avoids duplicate testing and unnecessary procedures, while improves the doctor patient relationship, decreases healthcare costs by helping employees take charge of their medical care and give them increased access to high quality medical professionals. In order for HIEs and RHIOs to achieve success there are several leading practices that need to be kept in mind. The first is engaging key stakeholders early on in the development process. Open and regular communication is very important. This will help develop trust and support among all the key players. RHIOs pose several challenges. The initial cost of purchasing or developing these systems is high. Uncertainty about who truly benefits from the RHIO may also cause confusion and a lack of interest, and limitation to regional data sharing stems from data security and privacy issues that exist (Shortliffe, 2006).

Advancements in medical informatics and the practical implementations of HIEs have benefitted the quality and quantity of infectious disease research. Electronic disease surveillance systems have allowed for the real time detection of potential outbreaks, (Kho et al., 2007) and have the further potential to be used for visualizing MRSA transmission across regions.
2.4.10 Significance

MRSA poses a significant public health challenge to all members of society including public officials who make policies, healthcare workers who treat and prevent MRSA, and average citizens who are at risk. The financial costs along with the quality of life costs are enormous (Gastmeier, 2010). It is an organism and infection seen in the hospital as well as the community, and continues to pose a threat. Numerous counter strategies have been developed and to some extent are working, however MRSA still continues to be a serious problem. New and novel techniques to combat this hearty organism are needed. With the advent and increased use of healthcare informational technology new strategies and greater understanding of this organism can be achieved.

The research outlined in this proposal aimed to examine risk factors associated with community associated MRSA, while also gaining an understanding of the molecular transmission of MRSA, both community and hospital acquired strains, across geographically distant hospitals. It achieves this by utilizing, leveraging, and enhancing existing partnerships between health networks and information technology resources.

This research has many potentially significant implications. First of all, it will test and enhance the existing protocols and information technology infrastructure by designing, creating and deploying the necessary foundations for an electronic HIE between multiple hospitals spread across a large regional geographic area. This will allow for the easy and safe transfer of healthcare information between hospitals. These hospitals will include seven small rural hospitals and one large academic medical center. The seven hospitals will hopefully be able to gain from the resources of the academic medical center. This sharing of information will augment collaboration and infectious...
disease surveillance, while upholding and maintaining the regulations pertaining to patient confidentiality, privacy and security laws. This is an extremely important aspect, as it will help to engage and stimulate best clinical practices in rural hospitals and bridge the digital divide between urban and rural hospitals. It will potentially also open the doors for further collaboration and exchange of healthcare information not just by hospitals but by other key stakeholders in the at-large community. It will also allow us to measure the proportion of MRSA, both hospital acquired and community associated cases, in rural hospitals, and give us a better appreciation of the risk factors involved in community associated MRSA cases, which are poorly understood. Understanding community associated MRSA is important as this type of MRSA is becoming the main mode of transmission and poses a serious threat to the health of the general public. Lastly, this research results in an increased understanding of the geospatial transmission of MRSA via different clonal types and by social means. This can eventually lead the discovery of novel methods to stop these modes of transmission and stay the burden of MRSA.
Chapter 3: Methods

3.1 Introduction

The overall purpose of this research study was to examine risk factors associated with community associated MRSA while also gaining an understanding of the molecular transmission of MRSA, both community and hospital associated strains, across geographically distant hospitals. The study employed a cross sectional observational study design, and utilized the resources and existing infrastructure of the Ohio State Health Network (OSHN), the Ohio State University Medical Center (OSUMC) Information Warehouse (IW) and OSUMC microbiology laboratory.

3.2 IRB approval and funding

This study was conducted with the approval and under the supervision of the Institutional Review Board (IRB) at the Ohio State University Office of Responsible Research Practices (ORRP). The study was of minimal risk to the participants and therefore an expedited review and waiver of consent were requested and approved by the IRB. Clinical MRSA positive isolates collected fell under the IRB category 5; “Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for non-research purposes (such as medical treatment or diagnosis)” (OSU ORRP, 2010). Member hospitals of the OSHN who did not have their own IRB deferred approval and oversight of the study to the Ohio State University IRB.
All research staff, including those at OSHN facilities, completed basic IRB and HIPAA training via the online Collaborative IRB Training Initiative (CITI) courses. Before beginning the study, a memorandum of understanding (MOU) was signed by the researchers and the hospitals detailing interactions, data sharing agreements, and other legal matters. A standard operating procedure (SOP) specifying the roles and responsibilities of the OSUMC, the outreach hospitals, and the OSU IRB was also drafted and signed by participating hospitals to ensure the ethical and moral conduction of research, and the safety of patients. Funding for this study was provided by the Center for Disease Control and Prevention (CDC) Epicenter’s program (cooperative agreement CI000328).

3.3 Specific Aim 1
3.3.1 Introduction

The purpose of specific Aim 1 of this study was to create an infection control collaborative and utilize the existing infrastructure and protocols of the OSHN and OSUMC IW to develop an electronic HIE between multiple hospitals spread across a large geographical area. This was achieved by leveraging the existing resources and creating new tools which allowed the safe exchange of health information.

3.3.2 Ohio State Health Network

The Ohio State Health Network is a 501 (c) 3 organization founded, in 1995 by the OSUMC, to create a partnership of rural hospitals throughout Ohio. It is a membership organization for which the primary task is to network, engage in resource sharing, and information exchange with the goal to reduce operating costs and increase the quality of care for patients (OSHN, 2010). It also provides a forum to identify and/or
develop best practices among rural hospitals in Ohio and the OSUMC. It has primarily focused on three improvement areas: clinical service, operational cost, and community health. At the time of this study, the OSHN consisted of eight hospitals. These included the following:

1. OSUMC, a 1191 tertiary care bed facility located in Columbus, Ohio which includes University Hospital Main and East, the James Cancer Center, the Ross Heart Hospital, and the Dodd rehabilitation hospital.

2. Barnesville Hospital, a 25 bed critical access hospital with 20 physicians located in Barnesville, Ohio.

3. Madison County Hospital, a 105 bed hospital with 50 physicians located in London, Ohio.

4. Wyandot Memorial Hospital, a 25 bed critical access hospital with 10 physicians located in Upper Sandusky, Ohio.

5. Mary Rutan Hospital, a 110 bed hospital with 116 physicians located in Bellefontaine, Ohio.

6. Bucyrus Community Hospital, a 25 bed critical access hospital with 29 physicians located in Bucyrus, Ohio.

7. Mercer Community Hospital, a 76 bed hospital with 84 physicians, located in Coldwater, Ohio.

8. Twin City Community Hospital, a 25 bed critical access hospital with 66 physicians located in Dennison, Ohio.
These hospitals range from a distance of 30 – 115 miles from the OSUMC, and from approximately 30 - 230 miles from each other. Figure 3.1 depicts a map of Ohio and the location of each the hospitals. Each of these hospitals is directly linked to the OSUMC intranet, OneSource, via a secure T1 fiber optic cable. This allows for resources to be shared among member facilities including policies, administrative and/or laboratory datasets, and educational materials. This also provides the interface needed for data transfer and entry critical to electronic surveillance and a HIE.

**Ohio State Health Network**

![Map of participating OSHN hospitals](image)

Figure 3.1. Map of participating OSHN hospitals (Hines et al., 2010)
3.3.3 OSUMC Information Warehouse

The OSUMC Information Warehouse (IW) is a comprehensive informatics platform supporting basic, clinical, and translational research. It is comprised of four integrated components: a clinical data repository comprised of over a million patients; a research data repository housing numerous research specific data; an application development platform for building business and research enabling applications; and a business intelligence environment assisting in reporting in all function areas (Kamal et al., 2010). Its architecture is based on four platforms, which include the acquisition, transfer and transformation, storage and management, and access of data. Figure 3.2 displays a schematic of the IW. It is an important tool for clinicians, researchers, and administrators because it enables them to collect, examine and analyze, data from different avenues within the medical system.

For ease of access, security, and management the data in the IW is organized into multiple subject centered repositories called data marts. These data marts collect data from numerous sources and store them in ready available and accessible formats. Data can be pulled and linked to each other simultaneously from several data marts for instant interchange and sharing of information. All patient health information in the IW is available in a de-identified form and access to the data marts is controlled and monitored in compliance with HIPAA regulations. Patient identifiers can be linked back to the data for studies where some identifiable data is needed (Erdal et al., 2008).

The IW has multiple tools for analysis that are available to meet individual reporting and data mining needs. Customized web applications can be created for both needs. Data entry applications are often created for those data elements that are not captured as part of any data
mart but are needed for analysis by users. The IW also uses Online Analytical Processing (OLAP) tools to provide a more complex view of aggregate data from multiple viewpoints. It is intended for high level or administrative use in trending/forecasting, financial modeling and risk analysis and provides advanced graphing and trending features. An important feature of the IW is the ad hoc query tool which allows for customized access to the most detailed level of information (Erdal et al., 2008). All of these tools were utilized in the development of the electronic HIE.

Figure 3.2. Schematic of OSUMC IW (Kamal et al., 2010)
3.3.4 Honest broker

In 2006, the OSU IRB recognized the OSUMC IW as an essential stakeholder and keeper of healthcare related data and thus designated it as an “honest broker.” The honest broker status allows the IW to “provide an OSU IRB approved process” and give researchers and administrators either coded or de-identified data without prior IRB approval for non-human subjects or exempt research (Lie et al., 2009).

The process of de-identification begins with the creation of a mirror or identical data mart. An automated software process combs through the data and de-links it from the identifiers. A second manual check to ensure the data is completely de-identified is also completed. The end result is an exact copy of the data but without the identifiers (Lie et al., 2009).

The honest broker status is an essential component of an electronic HIE in general and in particular to this study. By invoking this status, the OSUMC IW took full responsibility to store all identifiable specimen information from OSHN member organizations and transmit them for analysis in the form of a limited data set with HIPAA-defined personal health information (PHI) removed and no link back to patient identifiers, but yet still maintaining full dates, ages, and zip codes. This allowed for a detailed analysis while preserving patient confidentiality and privacy issues and being HIPAA compliant.

3.3.5 Database set up

All members of the OSHN are electronically linked to OSUMC via a secure T1 fiber optic cable, permitting each member access to the OSUMC intranet known as OneSource. This access allowed for a web based data entry portal and subsequent
database to be set up by means of OneSource. The benefit to having both the frontend
data entry portal and the backend stored database located via OneSource was that both
were located on the OSUMC servers and therefore behind the medical center’s firewall.
This ensured data security, protection, and compliance with federal privacy laws related
to patient’s rights and healthcare information. The OSUMC IW was the primary
developer and keeper of the database. The frontend of the database was located under the
Clinical Applications tab on OneSource. Each site had one or two individuals who were
approved by the IRB to collect, enter, transmit, and review the clinical and
epidemiological data of the participants. Each of these individuals was given a unique
user name and password by the OSUMC data security department. This let them securely
log on to the database. The database comprised of three separate entities linked together.
These included the application or face sheet data (the general demographics) entered in to
generate a de-identified code, the data from the data collection tool, and the
microbiological and molecular data from the MRSA specimens. The OSUMC
warehouses uses Oracle for their environment, thus all application data was stored in an
Oracle database, while the MRSA specimen data was stored in a set of joining tables.
The database was structured such that each entered specimen was given a unique random
code so that the data was kept de-identified. This way researchers analyzing the data
could look at what they needed while not viewing any identifiable patient data. However,
each OSHN member organization retained the ability to view all data, including patient
identifiers, for their own specimens. This gave the individual sites the flexibility to use
this data as a line listing of MRSA patients and also for other administrative purposes.
The website and web data collection tool were written using Microsoft C#, a basic yet
powerful type-safe, object-oriented language that allows programmers to build Windows applications, Web services, and database tools with ASP.Net, a Microsoft product that enables the development of web tools and services (Microsoft, 2011). All data was stored in an Oracle SQL Server database as an XML file containing both the questions and answers, but in separate databases. After all data was collected on a specimen, the user would hit the “submit” button. Once the data was submitted, Oracle automatically joined both XML files (questions and answers) and converted them into an exportable vertical table. This table had the ability to be exported via a search engine that was built into the IW Discover interface. Authorized users securely logged into Discover from the IW intranet and ran the data query. Log in could only occur on an OSUMC approved computer, which was behind the medical center’s firewall. Upon completion of the query the user had the option to export the entire table or detail specific variables to export.

3.4 Specific Aim 2
3.4.1 Introduction

The purpose of specific Aim 2 of this study was to estimate the proportion of community associated MRSA cases among all MRSA cases and examine the risk factors associated with community associated MRSA. Community associated MRSA cases in recent years have increased in number and overall proportion of isolated MRSA cases. They appear to be replacing traditional healthcare associated MRSA as the predominant strain (Popovich et al., 2008). Community associated MRSA infections occur in populations who do not have a known healthcare related exposure. Little is known about their proportion in hospitals, and specifically in rural hospitals, as well as their associated risk factors (Stevenson et al., 2005).
3.4.2 Data collection

Data collection for this portion of the study occurred at three distinct levels and locations. The first level was at the local hospital. The data collection form (appendix D) was filled out by the infection preventionist at each OSHN hospital excluding OSUMC. Due to the expected high number of cases from OSUMC a team of physicians and infection preventionists filled out the data collection form. To ensure quality and the same standard of collection, a data dictionary was developed explaining each data field. The second level of data collection occurred at the microbiology lab. The OSUMC microbiology lab conducted genotypical and molecular analysis on all collected MRSA isolates. If the need arose for more detailed or confirmatory analysis the samples were sent to other labs for further testing. The last level of data collection occurred at the OSUMC IW where system analysts gathered identified geospatial data and performed geographical information systems analysis.

3.4.3 Inclusion Criteria

Eligible participants included adult patients, defined as greater than or equal to 18 years, admitted to any of the OSUMC units including units in the University Hospital Main, OSU East Hospital, Ross Heart Hospital, and the James Cancer Hospital and/or OSHN hospitals during the study period who had a positive MRSA isolate. Out patients, including emergency room admissions, at the rural OSHN hospitals were also included. The study period was of one year in duration, from March 1st, 2009 to February 28th, 2010.
3.4.4 Exclusion Criteria

Patients who did not have a positive MRSA culture were excluded. Due to IRB restrictions, prisoners were also excluded.

3.4.5 Data collection process

The data collection process took place in eight steps and additionally involved the need, use, and resources of the OSUMC IW and OSUMC microbiology laboratory. The steps were:

Step 1: Patients with positive cultures for MRSA, from routine clinical culturing, were identified by the clinical microbiology laboratory for each OSHN hospital. The microbiology laboratory then notified the infection preventionist (IP) or designated contact about the culture. The infection preventionist reviewed the case to see if the patient met inclusion or exclusion criteria. The IP then went on to collect basic demographic data from all eligible patients. Demographic data collected for this step included: the hospital name, patient’s name, patient’s full address, data of birth, lab accession number, data and time of specimen, and the type of specimen. By securely logging into the database via OneSource the IP then entered the data. This triggered the generation of a de-identified code.

Step 2: Entering the basic demographic data into the database triggered the OSUMC IW via an automated process to generate a unique de-identified identification (ID) code, which was assigned and returned to the site investigator. The unique ID code for each patient was used for the collection and analysis of microbiologic samples and epidemiologic data. The key to this code was retained by the OSUMC IW under the
honest broker protocol. Thus this key was held by both the OSUMC IW and by the IP at each hospital, allowing them to use the data collected as infection control/quality data at their respected hospital. The retention of personal health information (PHI) may aid them in any quality analysis, including outbreak investigations. Once the IP had the de-identified code, they then proceeded with the remainder of the data collection on the case. The IP at any time could log out of the database and continue the data collection later. When they came back to enter in data at a later time, the IP had to securely re-log in.

Step 3: IPs asked their local microbiology laboratory (where the isolate was first cultured) to retain and send a sample of the isolate to the OSUMC Clinical Microbiology Laboratory via FedEx overnight shipping. FedEx supplies as well as microbiology slants and plates were given to the local microbiology laboratories. The isolates sent were void of any patient identifiers and only labeled by the de-identified code.

Upon receiving the isolate, the OSUMC Clinical Microbiology Laboratory performed rep-PCR testing on a portion of the isolate while freezing the rest in a -70 degree freezer for potential further analysis.

Step 4: Data collected by the IPs on each isolate/patient were entered via the web based data entry portal into a designated backend database housed in the OSUMC IW. By means of the honest broker protocol, data was linked to the unique ID code. Access and analyses was only to data that were coded with the PHI blinded or removed. Data entry into the database occurred either from hard copies of data collection forms by IW or other designated personnel or was entered directly from the web interface available to each site by securely logging in from OneSource.
Steps 5 and 6: If any of the isolates needed further molecular typing the OSUMC Clinical Microbiology Laboratory informed the OSU researchers, and then sent coded MRSA isolates to other labs such as, but not limited to, Ohio Department of Health (ODH) for PFGE typing. Agreements and arrangements with outside labs were made prior to sending any isolates. The labs tested the isolates and sent back the results. Any outside laboratory results were combined with the rep-PCR results on each coded isolate.

Step 7: The OSUMC Clinical Microbiology Laboratory forwarded all coded de-identified molecular and genotyping results on each MRSA isolate to the OSU researchers for subsequent input into the database.

Step 8: Approved OSU study personnel had an interface, including a search engine, within the MRSA database which permitted queries and analysis of all the data in the MRSA database. The PHI in the database was, however, blinded to the investigators and only the unique identification code was viewable. This database interface allowed for direct entry of the genotyping data. Alternatively, these data alongside geographical spatial data from specific Aim 3 were entered by the OSUMC IW personnel. Figure 3.3 highlights all steps and the entire process flow.
The genotypical testing of the collected MRSA isolates and their subsequent classification into colonial clusters was achieved by using the DiversiLab Microbial Typing System for the rep-PCR testing method. This system is designed and manufactured by Bacterial Barcodes, Inc. This system, developed in 2005, is a standardized and automated method of conducting rep-PCR DNA fingerprinting. The developers modified the lengthy and complex manual process by modifications of “rep-PCR chemistry and thermal cycling parameters, incorporation of microfluidics-based DNA amplicon fractionation and detection, and internet-based computer-assisted...
analysis, reporting, and data storage” (Healy et al., 2005). The system has been commercially available for the past several years.

All rep-PCR typing was conducted by the OSUMC microbiology laboratory’s trained technicians. The first step in this process was to extract the DNA from the collected MRSA isolates. After DNA extraction, rep-PCR primers were then used. These primers target and bind to multiple noncoding, repetitive sequences interspersed throughout the bacterial genome. Samples were then amplified using the DiversiLab Kit for DNA fingerprinting (Bacterial Barcodes, Inc. Athens, GA). The kit contains an instruction guide, which was precisely followed by the technician. The automated DiversiLab System then detects the rep-PCR products and analyses the virtual gel image creating a dendrogram. The software analyzes the electropherogram results of each individual isolate and compares the percentage of DNA similarity by comparing locations and intensities of individual peaks of one isolate to another isolate. Resulting bands illustrate the similarities between isolates. Isolates are clustered together by the software if there are 0-2 band differences. If there is a 3 or more band difference, the isolate is classified as a separate cluster. The DiversiLab System software also includes a genotype library where rep-PCR typed isolates are matched to a reference library of other genotypical and molecular typing methods such as PFGE and SCCmec typing. These additional matched molecular types obtained from the library were used in the analysis of the cases.

3.4.7 Variables

The purpose of this specific aim was to examine the risk factors associated with CA-MRSA. Thus the outcome variable was presence or absence of CA-MRSA. In this
study we collected only MRSA positive isolates. These isolates were classified into three categories; HA-MRSA, HACO-MRSA, or CA-MRSA. For the purposes of this study HA-MRSA was defined as a positive MRSA culture obtained greater than 48 hours after admission, with or without healthcare-associated risk factors. HACO – MRSA was defined as a positive MRSA culture obtained less than or equal to 48 hours after admission with identified healthcare-associated risk factors, while CA-MRSA was a positive MRSA culture obtained less than or equal to 48 hours after admission without healthcare-associated risk factors. Since both HA-MRSA and HACO MRSA are healthcare associated they were collapsed into one category HA-MRSA. Consequently, the outcome variable was CA-MRSA denoted as 1 compared to HA-MRSA, 0.

Other variables collected for this study, from the patient’s medical record, include those that were thought to play a clinical or significant role in the acquisition of MRSA. These included social demographic, clinical, laboratory, microbiological, epidemiological, and geospatial variables.

Social demographic variables included the categorical variables of gender and race. Family and social history variables regarding any alcohol use, history of smoking or incarceration were also included. Categorical healthcare-associated Risk Factors (HRF) in the 12 months preceding the positive culture which included presence of an invasive device (e.g., vascular catheter, G-tube), history of MRSA infection or colonization, surgery, hospitalization, dialysis, residence in a long-term care facility, or other co-morbid conditions such as diabetes mellitus, and AIDS were also examined.

Clinical variables included primary and secondary diagnosis, specific past medical history, specific past surgical history, presence of invasive devices in the past 7
days prior to infection and specifically which ones, and presence of a fever. The answers
to each of these variables were dichotomized as independent variable. Specific past
medical history included history of endocarditis, renal failure, cirrhosis, neoplasms,
immunosuppression, diabetes, chronic lung disease, transplantation, and AIDS. Specific
past surgical history included past trauma, orthopedic prosthesis and cardiac prosthesis.
Presence of invasive devices in the past 7 days included the following invasive devices:
hemodialysis, tracheostomy, endotracheal tube, mechanical ventilator, central venous
catheter, total parental nutrition therapy, Swan-Ganz catheter, foley catheter, and
drainage tubes.

All laboratory variables were continuous in nature and included specific values
for all aspects of a complete blood count, differential blood count, and a comprehensive
metabolic panel.

Microbiological variables primarily consisted of categorical variables depicting
antibiotic resistance to approximately 10 different antibiotics which included oxacillin,
erthyromycin, clindamycin, tetracycline, rifampin, moxifloxacin, gentamycin,
vancomycin, linezolid, quinupristine-dalfopristin, trimethoprin/sulfamethoxazole,
daptomycin, and nitrofurantoin. Categories were resistant, susceptible or intermediate.

Epidemiological variables included the date and time of culture, the date and time
of isolation, data and time of admission, length of stay, admitting hospital service, and
inpatient location which could be intensive care unit, patient care unit, or long term care
unit.

Geospatial variables included address, location and address prior to admission and
disposition at discharge.
The source of the isolate was recorded as, primary bacteremia where a catheter related or unknown source was present; secondary bacteremia such as a surgical site infection, lung infection, bone/joint infection, vascular, or soft-tissue infection; and other non-bacteremic infections such as skin/soft tissue, respiratory, urine, and all others other. Types of specimen included blood, sputum, urine, stool, or other. Outcomes for MRSA infection included the following:

1. cure - complete resolution of infection after completion of antibiotic treatment;

2. failure - persistence of infection and requirement of change in antibiotic therapy or additional intervention (blood culture growing MRSA ≥ 10 days after the collection of initial positive culture specimen and before completion of antibiotic therapy);

3. relapse resolution of infection after treatment and appearance of new symptoms and or positive culture, recurrent development of MRSA infection at the same site or a different site after ≥2 weeks after completion of antimicrobial therapy,

4. indeterminate - Unknown outcome, and

5. death – 30 days mortality due to any causes.

3.4.8 Sampling plan

3.4.8i Introduction

Two separate sampling plans resulting in the creation of two separate datasets were used. One dataset was used for the main risk factor analyses as a training dataset, while the other one was used as a validation dataset. Both data sets were combined
together for use in specific Aim 3. The reason for this sampling plan is to fulfill the necessary assumptions in the analysis of logistic regression and social networking.

3.4.8ii Sampling of MRSA isolates from OSHN hospitals

In order to gain an understanding of the true proportion and associated risk factors of CA-MRSA cases among all MRSA cases in smaller rural hospitals, all MRSA positive isolates from the seven OSHN outreach hospitals were sampled. This was for the main analysis.

3.4.8iii Sampling of MRSA isolates from OSUMC

The OSUMC averages approximately 1500 positive MRSA isolates each year. Collecting and genotyping all of these isolates was not feasible due to budget, time, and personnel restraints. Thus a random sample with the sampling frame being all MRSA positive isolates was employed.

The isolates sampled from OSUMC were used as the validation set for the risk factor analyses and were also used in the social networking analysis in specific Aim 3. Due to the nature of social networking analysis, further explained in the methods for specific Aim 3, it was important to collect isolates that are geographically and possibly socially linked to the other OSHN hospitals. A detailed discussion on the issue of non-independence of individuals and its effects on statistical analysis can be found in specific Aim 3. In order to achieve this OSUMC isolates were separated into two categories. The first category included those isolates that were targeted from the same zip codes as the catchment areas of the OSHN hospitals, while the second were OSUMC MRSA isolates
from non-targeted zip codes. A list was obtained from each of the OSHN hospitals
detailing the zip codes of their patient catchment area.

The OSUMC IW created a query that first identified all the finalized daily positive
MRSA cultures for admitted adults at the OSUMC. The query pulled the patient’s name,
medical record number as well as full address with zip code. The query then
automatically matched to the list of targeted zip codes. This query subsequently
generated two lists. The first list was those patients in targeted zip codes while the second
was those in non-targeted zip codes. The list was generated twice a week.

A key factor to social networking analysis is choosing subjects that are linked to each
other (Hanneman and Riddle, 2005). Due to this factor, we sampled all positive MSRA
isolates in the targeted zip codes. This was achieved by the researcher taking the IW
targeted list and first comparing it to a running line list of all previous patients to ensure
that no duplicates were sampled. The isolates from the targeted zip codes were noted and
the microbiology laboratory was notified to retain those isolates and begin rep-PCR
testing on them.

In the case of the non-targeted zip codes, a random sample was taken. The researcher
took the IW non-targeted zip code list and compared it to a running line list of all
previous patients to ensure that no duplicates were sampled. Based on available budget,
we estimated that rep-PCR analysis on approximately 13 non-targeted zip code patients
could be performed each week. We randomly choose 13 patients from the list of non-
targeted zip codes. In order to obtain which patients to choose from, each patient on the
list was given a number. A random generator then choose 13 numbers from the amount of
isolates. The isolates from the non-targeted zip codes were noted and the microbiology laboratory was notified to retain those isolates and begin rep-PCR testing on them.

3.4.9 Analysis
3.4.9i Proportion of CA-MRSA compared to HA-MRSA

Our study aimed to collect all MRSA positive isolates from the rural community outreach hospitals. Collecting all isolates gave us an understanding of the true proportion of CA-MRSA compared to HA-MRSA in rural hospitals.

3.4.9ii Risk factor analysis

Data collected from the outreach OSHN hospitals was used for the main risk factor analysis. Descriptive statistic, including frequencies and percentages, of CA-MRSA and HA-MRSA cases were generated first. To test whether there are any differences between both groups among variables chi-square test for categorical variables and t-test for continuous variables were used. Since our outcome or dependent variable was dichotomous (CA-MRSA vs. HA-MRSA) in nature, logistic regression was deemed the most appropriate to examine risk factors associated with CA-MRSA. This was done by first running a univariate model of all variables with CA-MRSA being the outcome variable. Any dichotomous variable with a chi square or continuous variable with a t-test p-value of less than 0.2 for the likelihood ratio was kept and utilized in the multivariable analysis.

The multivariable model building process employed forward selection to find a combination of variables that gave the best fit model. Addition of variables in the model was based on a significant p-value at the 0.05 alpha level from the difference of the likelihood ratios between the reduced and fuller model. When the likelihood ratio ceased
to give a significant p-value the model building was stopped. Interactions, if plausible, were to be tested once the best fit main effects model was built. Due to the excessive interaction combinations possible, only those variables with high biological plausibility were planned to be tested. Effect modification and confounding were planned to be tested for any of the interactions by examining a change in coefficient value with the addition of the interaction term.

One of the key assumptions to logistic regression is linearity in the logit. This was accessed by exploring either a smooth scatter plot or the fractional polynomials method depending on the number of independent variables. Appropriate diagnostic statistics were also tested in the model. If there were outliers, then these observations were to be removed one by one to see the effect on the coefficient. Any coefficients that changed the model by more than 20% were to be thrown out and a new model would be built from the data without the outlying observations.

The Hosmer-Lemeshow Goodness-of-fit test was tested on the final model to determine whether the predicted values are a good representation of the observed values.

The last step in the statistical analysis was to validate the model by testing the calibration and discrimination on a validation set. The validation set were the isolates collected from the OSUMC. The Hosmer-Lemeshow Goodness-of-fit test and a receiver operating characteristic (ROC) curve were used to determine this.

All data analysis was conducted using STATA10 and SAS. SAS9.2 was used for data cleanup and manipulation, while STATA10 was used for regression analysis.
3.5 Specific Aim 3
3.5.1 Introduction

The purpose of specific aim 3 of this study was to describe patterns of suspected intra-facility and inter-facility transmission of MRSA by evaluating epidemiological and geographic links by means of geographic information system and social network analysis.

3.5.2 Geographical Information Systems

3.5.2i Introduction

Geographical Information Systems (GIS) is defined as a system designed to capture, store, manipulate, analyze, manage and present all types of geographically referenced data (Foote and Lynch, 2000). For many years it has been used in population and environmental studies (Peuquet and Marble, 1990). In recent years studies have been published examining and employing the use of GIS software to track outbreaks and/or transmission of hospital acquired infections (Lee and Wong, 2010).

3.5.2ii Methods

Data being collected as part of this study included address of the patient at the time the specimen was collected. As this is a patient identifier the geocoding and generation of maps were to be completed by the honest broker i.e. the OSUMC IW. Analysts in the OSUMC IW will use the ESRI ArcGIS software suite to geocode all isolates in the stored MRSA research Oracle database tables, which are located on the IW servers. Address and clinical isolate information, such as rep-PCR type, PFGE type and infection site, were extracted to an Excel spreadsheet ArcCatalog was utilized to import
the Excel data into a geodatabase table from which the addresses were geocoded employing the U.S. Nationwide Streets address locator available from within ArcMap.

Maps and spatial data were generated by layering the shape files for the state, counties, zip codes and census tracts with the geocoded MRSA address data. Basic point maps differentiating the hospital with which the isolate was associated, as well as either the rep-PCR type or the infection site (e.g. blood, skin and soft tissue, sputum) by the use of different symbols and colors were generated. Graduated color maps were also developed to represent varying concentrations of isolates at both a county and a zip code level. Census tract data was loaded back into the MRSA research database table for further analysis.

3.5.3 Social Networking Analysis
3.5.3i Introduction to Social Networking Analysis

Orgnet, a social networking research firm, has defined social network analysis (SNA) as the mapping and measuring of relationships and flows between people, groups, organizations, computers or other information/knowledge processing entities (Orgnet, 2010). This allows for both a visual and computational analysis of how relationships and outcomes are linked to each other. According to Hanneman and Riddle in their textbook Introduction to Social Network Analysis (Hanneman and Riddle, 2005), SNA is the analysis of individuals and their relationship to each other. This is opposite to conventional and survey data analysis, which examines individuals and their attributes. In SNA, the individuals are known as actors depicted as nodes who exhibit relationships or ties with each other. Another key difference between SNA and conventional or survey analysis is that in SNA because researchers are looking for relationships, the actors are
not independently sampled. They are in fact chosen due to some known linkage between the actors, often within some naturally occurring boundary such as a zip code, neighborhood, or school. Thus SNA does not use sample populations, but instead uses censuses. To this date, there are no known methods for approximations of sampling distribution in SNA. Crouch and Wasserman in their “Practical guide to fitting p* Social Network Model via Logistic regression” note that because the assumption of independence in SNA models is not entirely valid, measures of likelihood statistics cannot carry a strict statistical interpretation. They can, however, be used as “a guide for evaluating model fitness” (Crouch and Wasserman M, 1997).

Social Network analysis has been used in the research of sexually transmitted diseases and tuberculosis infection to identify unrecognized patterns of transmission. By mapping out and visualizing epidemiological and demographic contact information data for each case and their contacts, connections between cases can be identified (Gardy et al., 2011). Application of this method to MRSA investigations can identify common links in health-care associated networks (e.g. hemodialysis unit, same outpatient clinic, common healthcare worker with MRSA colonization). Identification of new and unique transmission dynamics can and will consequently improve MRSA infection control guidelines and programs.

3.5.3ii Social networking software and analysis

Using identified MRSA clusters from the molecular genotyping in specific Aim 2 and from the GIS generated maps, specific clusters that appear to be linked to each other were chosen and further analyzed by means of social networking analysis. The criterion
for choosing the clusters was a combination of number of isolates in cluster, geographical location, PFGE type, and other interesting or relational variables. Data collected from the OSUMC is linked to the rural OSHN hospital by targeted zip code. This fulfills the criteria for SNA that data must be linked and not independent of each other. The social networking software UNICET was used. The software was developed by Steve Borgatti, Martin Everett and Lin Freeman and is distributed by Analytic Technologies. The freeware program NETDRAW which helps draw networks comes with UCINET (UCINET, ND, http://www.analytictech.com/ucinet). UCINET and NETDRAW were used to analyze the data for any social or demographic links between the patients and were graphed accordingly. Graphs depicted a node and its subsequent ties to other nodes. Figure 3.4 depicts a representation of nodes and ties from a sexual transmitted disease study.

Figure 3.4. Depiction of nodes and ties in a SNA (De et al., 2004)
Chapter 4: Methods for an infection control collaborative and health information exchange

4.1 Introduction

Infection control and proper surveillance play a critical role in the prevention and understanding of the transmission of hospital acquired infections (APIC, 2010). Infection control includes having relevant up-to-date policies and protocols, as well as a team of properly trained and dedicated individuals, and a culture and approach for patient safety. Successful surveillance is based on having a “clear, concise, and constant” surveillance definition in place and following “sound principles of epidemiology and statistics.” Using these principles the overall safety and quality of healthcare can be achieved.

Medical informatics is a fundamental component to improving the quality of healthcare (Weissman and Hasnain-Wynia, 2011) as it deals with all aspects of understanding and promoting the effective organization, analysis, management, and use of information in healthcare (AHRQ, 2002). Medical informatics has an extremely wide use and scope and includes decision support systems, information/knowledge retrieval systems, imaging and telemedicine systems, support of medical education, standards of interoperability, patient and public health information surveillance systems, electronic health records and electronic information exchanges. Over the years, medical informatics has developed into a robust and complex field that is focused not only on removing medical errors but also on the integration of electronically captured and exchangeable
data. However, due to the sensitivity and nature of the data being collected i.e. patient personal health data, the healthcare industry lags behind many other fields such as banking in full utilization of information technology to effectively and efficiently automate processes (Shortliffe, 2006).

Medical informatics, however, can be a very crafty research tool (President’s Council of Advisors of Science and Technology, 2010). It allows for multiple levels of information across disciplines to be leveraged in a short amount of time. In fact some data feeds can be real time (Eggers et al., 2007). Over the years medical informatics and healthcare technology have been used to generate novel techniques for surveillance and have in general enhanced the quality and breadth of infectious disease research. In a study examining the automated detection and reporting of notifiable diseases using EHRs, researchers at a Massachusetts hospital found that the EHR based surveillance system discovered a higher percentage of cases and at a quicker rate when compared to traditional passive surveillance techniques (CDC, 2008). Medical informatics has also played an innovative role in MRSA research. In study by Kho et al., the authors used computer generated log-in data and geographical information systems (GIS) software to document and map the contact patterns and transmission of MRSA between healthcare providers and patients. By creating detailed time sequence animations they were able to ascertain specific factors that contribute to the spread of hospital acquired infections such as using the same blood pressure cuff from one patient to another and the lack of proper isolation (Kho et al., 2006).

The HHS envisioned the federal government playing a key role in supporting and guiding the formation of HIEs and RHIOs (President’s Council of Advisors of Science
and Technology, 2010). They specifically recognized and addressed the issue of rural hospitals. Acknowledging that health disparities between urban and rural areas exist, they highlighted the need for a rural RHIO, possibly linked to an academic medical center or urban RHIO. This would reduce variability of care, increase knowledge and education among rural healthcare providers, and decrease the gap between communities (Thompson and Brailer, 2004). The IOM identifies several key initiatives that must be first adopted for rural RHIOs to take hold. These include adopting a rural community focus, developing consistent regulations and payment polices, assist collaborations and demonstrations in rural areas, and ensure high speed internet access to rural communities (IOM, 2005). In a study by Wang and colleagues, the authors compared the internet use among those who, for medical reasons, were limited in their ability to travel from rural and urban communities. They found that a digital divide existed between urban and rural residents (Wang et al., 2011). Urban residents had better access to information technology as well as increased knowledge and usage of computer systems. Having both this knowledge and access enables the patient to make better informed decisions about their healthcare, which in turn leads to better health. Thus the use of medical informatics in the delivery of health care plays an important role for prevention and treatment.

The HHS has also suggested that, in order to bridge the technology and knowledge gap between rural and urban medical facilities, rural hospitals should form formal partnerships with academic medical centers enabling both parties to share information and resources (President’s Council of Advisors of Science and Technology, 2010). In regards to infection control, this model of collaboration has been used by several academic medical centers and has had great success (Arora et al., 2010). One
such example is the Duke Infection Control Outreach Network (DICON), which is a part of the Duke University Medical Center (Anderson et al., 2011). DICON has a total of 39 hospitals in its network. In a recent study evaluating the impact of the network, Anderson et al. noted that for hospitals who had been in the network for at least 5 years there was a significant 50-70% decrease in MRSA infections. BJC hospital in St. Louis also found a similar decrease of infection rates in rural hospitals that partnered with it and the University of Washington in St. Louis (Murphy, 2002). Thus creating these networks or collaborations has great benefit for healthcare quality and patient safety (Meyer, 2005).

The goal of this study was to form an infection control collaborative and HIE between an academic medical center and several rural based hospitals, and allow for the exchange of healthcare data via electronic means with the idea of strengthening infection control policies and surveillance across hospitals in a large geographical area.

4.2 Methods

4.2.1 IRB approval and funding

This study was conducted with the approval and under the supervision of the Institutional Review Board (IRB) at the Ohio State University Office of Responsible Research Practices (ORRP). The study was of minimal risk to the participants and therefore an expedited review and waiver of consent was requested and approved. Collaborating hospitals without their own IRB were asked to defer approval and oversight of the study to the Ohio State University IRB. All research staff, including those at collaborating facilities, completed basic IRB and HIPAA training. Funding for this study was provided by the Center for Disease Control and Prevention (CDC) Epicenter’s program (cooperative agreement CI000328).
4.2.2 Settings and participants

Development of the infection control based HIE, between multiple hospitals spread across a large geographical area, was achieved by leveraging the existing infrastructure and protocols of the Ohio State Health Network (OSHN) and the Ohio State University Medical Center Information Warehouse (OSUMC IW). Utilizing these resources gave way to the creation of new tools allowing for the safe and secure exchange of health information.

4.2.3 Ohio State Health Network

The Ohio State Health Network is a 501 (c) 3 organization founded, in 1995 by the OSUMC, to create a partnership of rural hospitals throughout Ohio. It is a membership organization for which the primary task is to network, engage in resource sharing, and information exchange with the goal to reduce operating costs and increase the quality of care for patients (OSHN, 2010). It also provides a forum to identify and/or develop best practices among rural hospitals in Ohio and the OSUMC. It has primarily focused on three improvement areas: clinical service, operational, and community health. The OSHN at the time of our collaboration consisted of eight hospitals. These include the following:

1. The Ohio State University Medical Center, a 1191 tertiary care bed facility located in Columbus, Ohio which includes University Hospital Main and East, the James Cancer Center, the Ross Heart Hospital, and the Dodd rehabilitation hospital.

2. Barnesville Hospital, a 25 bed critical access hospital with 20 physicians located in Barnesville, Ohio.
3. Madison County Hospital, a 105 bed hospital with 50 physicians located in London, Ohio.

4. Wyandot Memorial Hospital, a 25 bed critical access hospital with 10 physicians located in Upper Sandusky, Ohio.

5. Mary Rutan Hospital, a 110 bed hospital with 116 physicians located in Bellefontaine, Ohio.

6. Bucyrus Community Hospital, a 25 bed critical access hospital with 29 physicians located in Bucyrus, Ohio.

7. Mercer Community Hospital, a 76 bed hospital with 84 physicians, located in Coldwater, Ohio.

8. Twin City Community Hospital, a 25 bed critical access hospital with 66 physicians located in Dennison, Ohio.

These hospitals range from a distance of 30 – 115 miles from the OSUMC, and from approximately 30 - 230 miles from each other. Figure 4.1 depicts a map of Ohio and the location of the hospitals. Each of these hospitals was directly linked to the OSUMC intranet, OneSource, via a secure T1 fiber optic cable. This allowed for resources to be shared among member facilities including policies, administrative and/or laboratory datasets, and educational materials. This also provided the interface needed for data transfer and entry, critical to electronic surveillance and a health information exchange.

A memorandum of understanding (MOU) was signed by the researchers and the hospitals detailing interactions, data sharing agreements, and other legal matters. A
standard operating procedure (SOP) specifying the roles and responsibilities of the OSUMC, the outreach hospitals, and the OSU IRB was also drafted and signed by the administrative authorities in the participating hospitals to ensure the ethical and moral conduction of research, and the safety of patients.

Figure 4.1. Map of participating OSHN hospitals (Hines et al., 2010)

4.2.4 OSUMC Information Warehouse

The OSUMC Information Warehouse (IW) is a comprehensive informatics platform supporting basic, clinical, and translational research. It is comprised of four integrated components: a clinical data repository holding over a million patients; a
research data repository housing numerous research specific data; an application
development platform for building business and research enabling applications; and a
business intelligence environment assisting in reporting in all function areas. Its
architecture is based on four platforms, which include the acquisition, transfer and
transformation, storage and management, and access of data. Figure 4.2 displays a
schematic of the IW. It is an important tool for clinicians, researchers, and administrators
that enables them to collect, examine and analyze, data from different avenues within the
medical system.

For ease of access, security, and management the data in the IW is organized into
multiple subject centered repositories called data marts. These data marts collect data
from numerous sources and store them in ready available and accessible formats. Data
can be pulled and linked to each other simultaneously from several data marts for instant
interchange and sharing of information. All patient health information in the IW is
available in a de-identified form and access to the data marts is controlled and monitored
in compliance with HIPAA regulations. Patient identifiers can be linked back to the data
for studies where some identifiable data is needed (Erdal et al., 2008).

The IW has multiple tools for analysis that are available to meet individual reporting
and data mining needs. Customized web applications can be created for both needs. Data
entry applications are often created for those data elements that are not captured as part of
any data mart but are needed for analysis by users. The IW also uses Online Analytical
Processing (OLAP) tools to provide a more complex view of aggregate data from multiple
viewpoints. It is intended for high level or administrative use in trending/forecasting,
financial modeling and risk analysis. It also provides advanced graphing and trending
features. An important feature of the IW is the ad hoc query tool which allows for customized access to the most detailed level of information (Erdal et al., 2008). All of these tools were utilized in the development of electronic health information exchange.

Figure 4.2. Schematic of OSUMC IW (Kamal et al., 2010)

4.2.5 Honest Broker Status and protocol

In 2006, the OSU IRB recognized the OSUMC IW as an essential stakeholder and keeper of healthcare related data and thus designated them as an “honest broker” The honest broker status allows the OSUMC IW to provide an OSU IRB approved process
and give researchers and administrators either coded or de-identified data without prior IRB approval for non-human subjects or exempt research (Lie et al., 2009).

The process of de-identification begins with the creation of a mirror or identical data mart. An automated software process combs through the data and de-links it from the identifiers. A second manual check to ensure the data is completely de-identified is also completed. The end result is an exact copy of the data but without the identifiers (Lie et al., 2009).

The honest broker status is an essential component of an electronic healthcare information exchange in general and in particular to this collaboration. By invoking this status, the OSUMC IW took full responsibility to store all identifiable specimen information from OSHN member organizations and transmit them for analysis in the form of a limited data set with HIPAA-defined PHI removed and no link back to patient identifiers, but yet still maintaining full dates, ages, and zip codes. This allowed for a detailed analysis, while preserving patient confidentiality and privacy issues, and maintaining HIPAA compliance.

4.2.6 Health Information Exchange Design

All members of the OSHN are electronically linked to OSUMC via a secure T1 fiber optic cable, permitting each member access to the OSUMC intranet known as OneSource. This access allowed for a web based data entry portal and subsequent database to be set up by means of OneSource. The benefit to having both the frontend data entry portal and the backend stored database located via OneSource was that both were located on OSUMC servers and therefore behind the medical center’s firewall. This ensured data security, protection, and compliance with federal privacy laws related to
patient’s rights and healthcare information. The OSUMC IW was the primary developer and keeper of the database. The frontend of the database was located under the Clinical Applications tab on OneSource. Each site had one or two individuals who were approved by the IRB to collect, enter, transmit, and review the clinical and epidemiological data of their hospital’s cases. Each of these individuals was given a unique user name and password, by the OSUMC data security department, allowing them to securely log on to the database. The database comprised of three separate entities linked together. These included the application or face sheet data (the general demographics), entered in to generate a unique patient specific de-identified code which would be used for further data entry and analysis, the data from the data collection tool, and the microbiological and molecular data from the MRSA specimens. The OSUMC IW’s environment is Oracle based, thus all application data were stored in an Oracle database, while the MRSA specimen data were stored in a set of joining tables. The database was structured such that each entered specimen was given a unique random code so that the data is kept de-identified. This way researchers analyzing the data could look at what they needed while not viewing any identifiable patient data. However, each OSHN member organization retained the ability see all data, including patient identifiers, for their own specimens and facility. OSHN members were only able to see their facility’s data. This gave the individual sites the flexibility to use this data as a line listing of MRSA patients and also for other administrative purposes. The website and web data collection tool were written using Microsoft C#, a basic but powerful type-safe, object-oriented language that allows programmers to build Windows applications, Web services, and database tools (Microsoft, 2011) with ASP.Net, a Microsoft product that enables the development of
web tools and services (Microsoft, 2011). All data was stored in an Oracle SQL Server database as an XML file containing both the questions and answers, but in separate databases. After all data was collected on a specimen, the user would hit the “submit” button. Once the data was submitted, Oracle automatically joined both XML files (questions and answers) and converted them into an exportable vertical table. This table had the ability to be exported via a search engine that was built into the IW Discover interface. Authorized users securely logged into discover from the IW intranet and ran the data query. Log in could only occur on an OSUMC approved computer which is behind the medical center’s firewall. Upon completion of the query the user had the option to export the entire table or detail specific variables to export. Export formats included csv, excel, and html files. The database and tools were used to collect detailed information on all positive MRSA cases that were seen, both in and out patient, in all 8 hospitals (the OSUMC and 7 OSHN member hospitals).

4.3 Results

In the summer of 2008, a meeting was held with the OSHN Board of Directors to propose the idea of the partnering together with the OSUMC to create an infectious disease research collaborative, focused on standardizing infection control practices and surveillance while increasing cooperation with research projects. A main focus of the collaborative was to conduct research to understand the different molecular genotypes of MRSA and its transmission within and between hospitals. OSU researchers explained to the board the complexity and virulence of MRSA as well as its consequences to the hospitals and general public, and why it was necessary to create such a collaborative. A key selling point to the Board was the benefit of being able to bridge the knowledge and
technology gap between the rural hospitals and an academic medical center as well as the
ability to share resources with a large academic medical center. The seven member
OSHN Board of Directors understood the need and potential of the collaborative and
agreed.

Meetings were set up with the OHSN executive director to discuss legalities,
logistics and available resources. A memorandum of understanding (MOU) to be sign
between the OSHN hospitals and the OSU researchers was drafted and signed by each
OSHN individual member. The MOU draft can be found in Appendix A.

Also in 2008, an infection preventionist (IP) was hired by the OSU researchers to
act as the liaison between OSU and the OSHN participating members. The IP’s primary
responsibilities were to help standardize methods of data collection, align policies with
correct practice, conduct and lead educational roundtable meetings and trainings with the
hospitals, giving education on MRSA and infection control and prevention, and serves as
a liaison between OSU researchers and infection control practitioners at the outreach
hospitals.

The OSU researchers visited each hospital and presented the proposal to hospital
administration and infection control staff, in order to get their feedback and buy in. The
site visit also served as a means to gain an understanding and assessment of their
procedures, policies, surveillance parameters, microbiology and information technology
infrastructure and capabilities, and their ability to work in the network. The sites were
verified to have a working T1 connection and access to the OSU intranet, OneSource.
Evaluations were made in terms of current practices and methods for infection control
data collection, and information technology infrastructure and support.
At the same time OSU researchers met with the OSU IRB to finalize logistics for the study. Using an IRB template, a study and site specific standard operating procedure (SOP) was created. This detailed the roles and responsibilities of the OHSN hospitals and the OSU researchers. The SOP was signed by the responsible parties in the member hospitals and by the OSU researchers. The SOP template, as designed by the OSU research team and IRB, can be found in Appendix B. Each hospital then proceeded to apply for a federal wide assurance (FWA) number, allowing them to legally conduct research. The hospitals listed themselves as research sites of OSU with the IRB on record also as OSU, thereby deferring all IRB issues to the OSU IRB.

As the hospitals were awaiting the FWA numbers and IRB approval, the OSUMC IW created the database. The database was created in stages using a series of beta sites. OSU researchers utilized these beta sites to refine functionality and use of the database. All eight members of the OSHN received training on database functionality and use by the OSU infection preventionist and were successfully able to log in and utilize the database. The OSHN hospitals began using the database on March 1st, 2009.

Table 4.1 highlights some general and infection control characteristics of the rural hospitals. A total of 1761 MRSA isolates, 1263 from OSU and 498 from outreach hospitals, were logged into the database over 15 month time frame (March 2009 – June 2010). OSU isolates included 500 that had been retrospectively collected and banked by the OSUMC Microbiology Laboratory. Basic patient information for these isolates was directly merged from the microbiology lab systems to the database. Each hospital was able to only view their data while, OSU researchers were able to view and export all data into a de-identified format. Addresses and identifiable information from OSHN member
hospitals were not available to OSU researchers. The database served as an online line listing of MRSA cases for member’s hospitals and was often used for administrative purposes. For OSU researches that database served as online secure data repository.

A quarterly round table discussion took place between OSU and the 7 OSHN hospitals regarding study issues, updates, and general infection control practices. These updates were chaired by the IP. Periodically, the OSU researchers would travel to the OSHN sites to give updates to them regarding interim and final findings. Continuing medical education credits were given to participants of these presentations.

4.4 Discussion

The goal of this study was to form an infection control collaborative and HIE between an academic medical center and several rural based hospitals, and allow for the exchange of healthcare data via electronic means with the idea of strengthening infection control policies and surveillance across hospitals in a large geographical area.

The successful creation of the infection control collaboration and implementation of the HIE is based on several factors. First and foremost, time and effort were exerted on getting the key stakeholders, both the OSHN Board and the specific hospital’s administration and staff, committed to the collaborative. In order to facilitate a smooth relationship, an IP was hired in to help with knowledge transfer and logistics. This created a cordial atmosphere and a sense of peer to peer collaboration or knowledge sharing instead of the feeling of being mandated by an outside organization. Creating a framework of partnership between all participants is critical to the success of any collaborative between rural and academic medical centers (Meyer, 2005).
Another key factor in the implementation of the HIE is the use of the honest broker status. Issues with data security and privacy have always been a barrier to the implementation of EHRs and the use of health information technology (HIT). It is important to have developed policies as to who gets access and at what level do they have access to. Safe guards and mechanisms need to be in place as to how much information is shared and by whom. Computer systems must have secure log-ons that are audited from time to time to keep a system of checks and balances (Shortliffe, 2006). The honest broker status allowed for the collection and use of identified data because it was guaranteed not to be shared with those not authorized to view it and because it was safe behind the firewall. The honest broker protocol gives the possibility of creating research consortiums with multiple key stakeholders in the at-large community.

The seven hospitals will hopefully be able to gain from the resources of the academic medical center. This sharing of information will augment collaboration and infectious disease surveillance, while upholding and maintaining the regulations pertaining to patient confidentiality and privacy laws. This is an extremely important aspect, as it will help to engage and stimulate best clinical practices in rural hospitals and bridge the digital divide between urban and rural hospitals.

4.4 Conclusions

Infection control and proper surveillance plays a critical role in the prevention and understanding of the transmission of hospital acquired infections. It is important to comprehend best practices and ensure that they are implemented. One method of ensuring this is forming collaboration between institutions. Specifically collaboration between academic medical centers and rural hospitals, as this will help bridge the
knowledge and technology gap. One key tool to successfully facilitating collaboration is the use of HIT. Health information technology has progressed and developed tremendously since its introduction into the field of medicine several decades ago. The use of HIT is no longer an anomaly but is in fact the norm and a necessity to safely, effectively and efficiently treat patients. By utilizing and enhancing existing resources, protocols, and information technology infrastructure health information exchanges can be developed. This will allow for the easy and safe transfer of healthcare information between hospitals. This sharing of information will augment collaboration and infection surveillance, while upholding and maintaining the regulations pertaining to patient confidentiality and privacy laws. This is an extremely important aspect, as it will bridge the information technology divide between rural and urban hospitals, and will potentially open the doors for further collaboration and exchange of healthcare information not just by hospitals but by other key stakeholders in the at-large community.
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Table 4.1 Infection control characteristics of the rural hospitals for 2007
Chapter 5: Proportion and Risk Factor analysis of CA-MRSA within Rural Hospitals

5.1 Introduction

For thousands of years bacterial infections have been a major cause of death in the world (Forrest, 1982). Cultural and homemade treatments and remedies from honey to herbs existed and were frequently, yet on a small scale, beneficial. However, it was not until the discovery of antimicrobial agents in the mid 1800’s and their mass production in the early 1900’s that societal progress in the treatment and prevention of bacterial infections gained strength. With the discovery, by Fleming of penicillin in 1927, and its rampant use in the treatment of *Staphylococcus aureus* (SA) infections, also came the overuse and abuse of penicillin (Jeśman et al., 2011). By 1959, all SA infections were resistant to penicillin, thus leading to the discovery and use of methicillin as the drug of choice for SA infections. However, within a couple of years of its introduction, methicillin resistant SA (MRSA) was discovered. Ever since, MRSA has become a significant multidrug resistant organism (MDRO) that has increased to epidemic and endemic levels. It is regarded as the most common healthcare-associated infection (HAI) (Chambers, 2001). MRSA has been a formidable foe over the last couple of decades as it accounts for more than 278,000 hospitalizations and 56,000 septic episodes annually (National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, 2004, p 470). It has been the focus of countless
campaigns and prevention strategies due to its high mortality and morbidity rate. It increases length of stay in hospitals which may result in continued transmission among patients and healthcare workers (Cosgrove et al., 2005).

Community acquired MRSA cases in recent years have increased in number and overall proportion of isolated MRSA cases. They appear to be replacing traditional healthcare associated MRSA as the predominant strain (Popovich et al., 2008). Community acquired MRSA infections occur in populations who do not have a known healthcare related exposure. Little is known about their proportion in hospitals, and specifically in rural hospitals, as well as their associated risk factors (Stevenson et al., 2005). It is essential to not only measure the prevalence and proportion of both hospital and community associated MRSA, but also to examine the risk factors associated with these types of infections. The goal of this study was to estimate the proportion of community associated MRSA cases among all MRSA cases from multiple rural hospitals and examine the risk factors associated with community acquired MRSA.

5.2 Methods

5.2.1 IRB approval and funding

This study was conducted with the approval and under the supervision of the Institutional Review Board (IRB) at the Ohio State University Office of Responsible Research Practices (ORRP). The study was of minimal risk to the participants and therefore an expedited review and waiver of consent was requested and approved. Clinical MRSA positive isolates collected fall under IRB category 5; “Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for non-research purposes (such as medical treatment or diagnosis)”
OSU ORRP, 2010). Collaborating hospitals without their own IRB were asked to defer approval and oversight of the study to the Ohio State University IRB. All research staff, including those at collaborating facilities, completed basic IRB and HIPAA training by enrolling in the online Collaborative IRB Training Initiative (CITI) courses. A memorandum of understanding (MOU) was signed by the researchers and the hospitals detailing interactions, data sharing agreements, and other legal matters. A standard operating procedure (SOP) detailing the roles and responsibilities of the Ohio State University Medical Center (OSUMC), the outreach hospitals, and the OSU IRB was drafted and signed by participating hospitals to ensure the ethical and moral conduction of research, and the safety of patients. Funding for this study was provided by the Center for Disease Control and Prevention (CDC) Epicenter’s program (cooperative agreement CI000328).

5.2.2 Study design and setting

This study employed a cross sectional observational design. It was conducted at the OSUMC and 7 rural outreach hospitals collectively known as the Ohio State Health Network (OSHN). A detailed description of the OSHN and these hospitals can be found in chapters 3 and 4.

5.2.3 Inclusion Criteria

Eligible participants included adult patients, defined as greater than or equal to 18 years, admitted to any of the OSUMC units including units in the University Hospital Main, OSU East Hospital, Ross Heart Hospital, and the James Cancer Hospital and/or OSHN hospitals during the study period who had a positive MRSA isolate. Outpatients, including emergency room admissions, at the OSHN hospitals were also included. The
data collection for this study occurred over a one year time period (March 2009 – March 2010).

5.2.4 Exclusion Criteria

Patients who did not have a positive MRSA culture and/or were treated as an outpatient at the OSUMC were excluded from the study. Due to IRB restrictions, prisoners were also excluded.

5.2.5 Data collection process

Data collection for this study occurred at three distinct levels and locations. The first level was at the local hospital. The infection preventionist at each OSHN hospital was responsible for data collection and entry. Due to the high number of cases from OSUMC a team of physicians and infection preventionists (IP) filled out the data collection form. To ensure quality and the same standard of collection, a data dictionary was developed explaining each data field. The second level of data collection occurred via the microbiology lab. The OSUMC microbiology lab conducted genotypical and molecular analysis on all (OSUMC and OSHN member hospitals) collected MRSA isolates. Samples were also sent to other labs for more detailed or confirmatory analysis, if and when needed. The last level of data collection occurred at the OSUMC IW where system analysts collated identified geospatial data and performed geographical information systems analysis.

The process for data collection took place in eight steps. The steps can be summarized as the following:

Step 1: Patients with positive cultures for MRSA, from routine clinical culturing, were identified by the clinical microbiology laboratory for each OSHN hospital. The
The microbiology laboratory then notified the IP or designated contact person about the culture. The IP reviewed the case to see if the patient met inclusion or exclusion criteria. If the patient met inclusion criteria the IP then proceeded to collect basic demographic data. The demographic data for this step included: the hospital name, patient’s name, patient’s full address, data of birth, the lab ascension number, date and time of specimen, and the type of specimen. The IP subsequently logged in and entered the data into the secure database via the OSUMC intranet, OneSource, which triggered the generation of a de-identified code.

Step 2: Entering the basic demographic data into the database triggered the OSUMC IW via an automated process to generate a unique de-identified identification (ID) code, which was assigned and returned to the site investigator. Appendix F, as designed by the OSU research team, details the instruction on how to obtain the de-identified code. The unique ID code for each patient was then used for the collection and analysis of microbiologic samples and epidemiologic data. The OSUMC IW under the honest broker protocol retained the key to the code for all subjects, while the IP at each hospital also retained the code for their specific patients, allowing them to use the data collected for infection control/quality purposes such as outbreak investigations, at their respected hospital. Obtaining the de-identified code allowed the IP to proceed with the remainder of the data collection on the case.

Step 3: IPs then asked their local microbiology laboratory (where the isolate was first cultured) to retain and send a sample of the isolate to the OSUMC Clinical Microbiology Laboratory via overnight shipping. Shipping supplies as well as microbiology slants and plates were provided to the local microbiology laboratories. The
isolates were sent void of any patient identifiers and only labeled by the de-identified code.

The OSUMC Clinical Microbiology Laboratory received the isolate, stored and performed rep-PCR testing on a portion of the isolate while freezing the rest in a -70 degree freezer for potential further analysis.

Step 4: Data collected by the IPs on each isolate/patient was entered via the web based data entry portal into a designated backend database housed in the OSUMC IW. By means of the honest broker protocol, the data was linked to the unique ID code. Access and analyses by OSU researchers was only to coded data with the PHI blinded or removed. Data entry into the database occurred both from hard copies of data collection forms by IW or other designated personnel and directly from the web interface available to each site by securely logging in from OneSource.

Steps 5 and 6: The OSUMC Clinical Microbiology Laboratory informed the OSU researchers if any of the isolates needed further molecular typing. If so, they then sent coded MRSA isolates to other labs such as, but not limited to, the Oho Department of Health (ODH) for PFGE typing. Agreements and arrangements with outside labs were made prior to sending any isolates. The labs tested the isolates and sent back the results.

Step 7: The OSUMC Clinical Microbiology Laboratory forwarded all molecular and genotyping results on each MRSA isolate to the OSU researchers for subsequent input into the database. These data were coded using the de-identified code and were also devoid of any PHI.

Step 8: Approved OSU study personal using an interfaced search engine via the database, merged, queried and analyzed all of the data in the MRSA database. The PHI
in the database was however, blinded to the investigators. Figure 5.1 highlights all steps and the entire process flow.

![MRSA Project Process Flow](image)

Figure 5.1. Process flow for data collection (Hines et al., 2010)

5.2.6 Molecular techniques

The genotypical testing of the collected MRSA isolates and their subsequent classification into clonal clusters was accomplished by means of rep-PCR testing.

Rep-PCR testing was completed by using the DiversiLab Microbial Typing System by Bacterial Barcodes, Inc. This system, developed in 2005, is a standardized and automated method of conducting rep-PCR DNA fingerprinting. The developers modified the lengthy and complex manual process by modifications of “rep-PCR chemistry and
thermal cycling parameters, incorporation of microfluidics-based DNA amplicon fractionation and detection, and internet-based computer-assisted analysis, reporting, and data storage” (Healy et al., 2005). The system has been commercially available for the past several years.

All rep-PCR typing was conducted by the OSUMC microbiology laboratory’s trained technicians. The first step in this process was to extract the DNA from the collected MRSA isolates. After DNA extraction, rep-PCR primers were then used. These primers target and bind to multiple noncoding, repetitive sequences interspersed throughout the bacterial genome. Samples were then amplified using the DiversiLab Kit for DNA fingerprinting (Bacterial Barcodes, Inc. Athens, GA). The kit contained an instruction guide, which was precisely followed by the OSU technicians. The automated DiversiLab System then detected the rep-PCR products and analyzed the virtual gel image creating a dendrogram. The software analyzed the electropherogram results of each individual isolate and compared the percentage of DNA similarity by matching locations and intensities of individual peaks of one isolate to another isolate. Resulting bands illustrated the similarities between isolates. Isolates were clustered together by the software if there are 0-2 band differences. If there were 3 or more band differences, the isolate were classified as a separate cluster. The DiversiLab System software also included a genotype library where rep-PCR typed isolates were matched to a reference library of other genotypical and molecular typing methods such as PFGE and SCCmec typing.
5.2.7 Variables

The purpose of this study was to examine the risk factors associated with CA-MRSA. Thus the outcome or dependent variable is presence or absence of CA-MRSA. Only MRSA positive isolates were collected. These isolates were classified into three categories; HA-MRSA, HACO-MRSA, or CA-MRSA. For the purposes of this study HA-MRSA was defined as a positive MRSA culture obtained greater than 48 hours after admission, with or without healthcare-associated risk factors. HACO – MRSA was defined as a positive MRSA culture obtained less than 48 hours after admission with identified healthcare-associated risk factors, while CA-MRSA was a positive MRSA culture obtained less than 48 hours after admission without healthcare-associated risk factors. Since both HA-MRSA and HACO MRSA are healthcare associated they were collapsed into one category HA-MRSA. Consequently, the outcome variable was CA-MRSA denoted as 1 compared to HA-MRSA, 0.

Other variables collected for this study included those that are thought to play a clinical or significant role in the acquisition of MRSA and included social demographic, clinical, laboratory, microbiological, epidemiological, and geospatial variables.

Social demographic variables included the categorical variables of gender and race. Family and social history variables regarding any alcohol use, history of smoking or incarceration were also included. Categorical healthcare-associated risk factors (HRF) in the 12 months preceding the positive culture which included presence of an invasive device (e.g., vascular catheter, G-tube), history of MRSA infection or colonization, surgery, hospitalization, dialysis, and residence in a long-term care facility were also examined.
Clinical variables included primary and secondary diagnoses, specific past medical history, specific past surgical history, presence of invasive devices in the past 7 days prior to infection and specifically which ones, and presence of a fever. Specific past medical history included co-morbid conditions such as history of endocarditis, renal failure, cirrhosis, neoplasms, immunosuppression, diabetes, chronic lung disease, transplantation, and AIDS. Specific past surgical history included past trauma, orthopedic prosthesis and cardiac prosthesis. Presence of invasive devices in the past 7 days included the following invasive devices: hemodialysis, tracheostomy, endotracheal tube, mechanical ventilator, central venous catheter, total parental nutrition therapy, Swan-Ganz catheter, foley catheter, and drainage tubes.

All laboratory variables were continuous in nature and included specific values for all aspects of a complete blood count, differential blood count, and a comprehensive metabolic panel.

Microbiological variables primarily consisted of categorical variables depicting antibiotic resistance to approximately 10 different antibiotics which included oxacillin, erythromycin, clindamycin, tetracycline, rifampin, moxifloxacin, gentamycin, vancomycin, linezolid, quinupristine-dalfopristin, trimethoprin/sulfamethoxazole, daptomycin, and nitrofurantoin. Isolates were resistant, susceptible or intermediate.

Epidemiological variables included the date and time of culture, isolation, and of admission. Length of stay, admitting hospital service, and inpatient location which could be intensive care unit, patient care unit, or long term care unit was also assessed.

Geospatial variables included address, location and address prior to admission and disposition at discharge.
The source of the isolate was recorded as, primary bacteremia where a catheter related or unknown source was present; secondary bacteremia such as a surgical site infection, lung infection, bone/joint infection, vascular, or soft-tissue infection; and other non-bacteremic infections such as skin/soft tissue, respiratory, urine, and all others. Types of specimen included blood, sputum, urine, stool, or other. Outcomes for MRSA infection comprised of the following:

1. cure - complete resolution of infection after completion of antibiotic treatment;

2. failure - persistence of infection and requirement of change in antibiotic therapy or additional intervention (blood culture growing MRSA less than 10 days after the collection of initial positive culture specimen and before completion of antibiotic therapy);

3. relapse resolution of infection after treatment and appearance of new symptoms and or positive culture, recurrent development of MRSA infection at the same site or a different site after greater than or equal to 2 weeks after completion of antimicrobial therapy,

4. indeterminate - Unknown outcome, and

5. death – 30 days mortality due to any causes.

Appendix D, designed by the OSU research team, contains the complete data collection form and data dictionary.
5.2.8 Sampling plan

5.2.8i Introduction

Two separate sampling plans were used to create two separate datasets. One dataset was used for the main risk factor analyses, while the other one was used as a validation dataset. Both data sets were combined together for use in a separate social networking data analysis (see chapter 3 and 6 for details). The reason for this sampling plan was to fulfill the necessary assumptions in the two separate analyses of logistic regression and social networking.

5.2.8ii Sampling of MRSA isolates from OSHN hospitals

In order to gain an understanding of the true proportion and associated risk factors of CA-MRSA cases among all MRSA cases in smaller rural hospitals, all MRSA positive isolates from the seven OSHN outreach hospitals were sampled. This sample was used for the main analysis.

5.2.8iii Sampling of MRSA isolates from OSUMC

The OSUMC averages approximately 1500 positive MRSA isolates each year. Collecting and genotyping all of these isolates was not feasible due to budget, time, and personnel restraints. Thus a random sample with the sampling frame being all MRSA positive isolates was used.

The isolates sampled from OSUMC were used as the validation set for the risk factor analyses and were also used in the social networking analysis. Due to the nature of social networking analysis, as noted in chapters 3 and 6, it is important to collect isolates that are geographically and possibly socially linked to the other OSHN hospitals. A detailed discussion on the issue of non-independence of individuals and its effects on statistical
analysis can also be found in chapters 3 and 6. In order to achieve this OSUMC isolates were separated into two categories. The first category were those isolates that were targeted from the same zip codes as the catchment areas of the OSHN hospitals, while the second were the OSUMC MRSA isolates from the non-targeted zip codes. A list was obtained from each of the OSHN hospitals detailing the zip codes of their patient catchment area.

The OSUMC IW created a query that first identified all the finalized daily positive MRSA cultures for admitted adults at the OSUMC. The query pulled the patient’s name, medical record number as well as full address with zip code. The query then automatically matched to the list of targeted zip codes. This query subsequently generated two lists. The first list was those patients in targeted zip codes while the second was those in non-targeted zip codes. The list was generated twice a week. Appendix E, designed by the OSU research team, gives the instructions on how to obtain the list of OSUMC positive MRSA cases.

A key factor to social networking analysis is choosing subjects that are linked to each other (Hanneman and Riddle, 2005). Due to this factor, all positive MSRA isolates in the targeted zip codes were sampled. This was achieved by the researcher taking the IW targeted list and first comparing it to a running line list of all previous patients to ensure that no duplicates were sampled. The isolates from the targeted zip codes were noted and the microbiology laboratory was notified to retain those isolates and begin rep-PCR testing on them.

In the case of the non-targeted zip codes, a random sample was taken. The OSU researchers took the IW non-targeted zip code list and again compared it to a running line
list of all previous patients to ensure that no duplicates were sampled. Based on available
budget, it was estimated that rep-PCR analysis could be performed on approximately 13
non-targeted zip code patients each week. A random sample of 13 patients from the list of
non-targeted zip codes was thus chosen each week. In order to determine which patients
to choose, each patient on the list was given a number and a random generator then chose
13 numbers from the amount of isolates. The isolates from the non-targeted zip codes
were noted and the microbiology laboratory was notified to retain those isolates and
begin rep-PCR testing on them.

5.2.9 Analysis

5.2.9i Proportion of CA-MRSA compared to HA-MRSA

This study aimed to collect all MRSA positive isolates from the 7 rural
community outreach hospitals. Collecting all isolates gave an understanding of the true
proportion of CA-MRSA compared to HA-MRSA in rural hospitals.

5.2.9ii Risk factor analysis

Data collected from the outreach OSHN hospitals was used for the main risk
factor analysis. Descriptive statistics, including frequencies and percentages, of CA-
MRSA and HA-MRSA cases were generated first. To test whether there were any
differences between both groups with respect to the variables of interest, chi-square test
for categorical variables and t-test for continuous variables were conducted. Since the
outcome or dependent variable was dichotomous (CA-MRSA vs. HA-MRSA) in nature,
logistic regression was employed to examine risk factors associated with CA-MRSA. The
first step in this process was to run a univariate model of all variables with CA-MRSA
being the outcome. Any dichotomous variable with a chi square or continuous variable
with a t-test p-value of less than 0.2 for the likelihood ratio was then retained and utilized in the multivariable analysis.

The multivariable model building process used stepwise forward selection to find a combination of variables that gave the best fit model. Addition of variables in the model was based on a significant p-value at the 0.05 alpha level from the difference of the likelihood ratios between the reduced and fuller model. When the likelihood ratio ceased to give a significant p-value the model building was stopped. Interactions were to be tested once the best fit main effects model was built. Due to the excessive interaction combinations possible, only those variables with high biological plausibility were to be tested. Effect modification and confounding were also to be tested for any of the interactions by examining a change in coefficient value with the addition of the interaction term.

One of the key assumptions to logistic regression is linearity in the logit. This was to be accessed by exploring either a smooth scatter plot or the fractional polynomials method depending on the number of independent variables. Appropriate diagnostic statistics including leverage, change in deviance, and influence were also tested in the model.

The Hosmer-Lemeshow Goodness-of-fit test was assessed on the final model to determine whether the predicted values are a good representation of the observed values.

The last step in the statistical analysis was to validate the model by testing the calibration and discrimination on a validation set. The validation set were the isolates collected from the OSUMC. The Hosmer-Lemeshow Goodness-of-fit test and a receiver operating characteristic (ROC) curve were used to determine this.
All data analysis was conducted using STATA10 and SAS. SAS9.2 was used for data cleanup and manipulation, while STATA10 was used for regression analysis.

5.3 Results

5.3.1 Dataset and Descriptive statistics

Over a one year time period, from March 2009 to March 2010, a total of 1024 MRSA isolates were collected. Rep-PCR analysis was performed on all isolates. Among the 1024, 625 were from the OSUMC while 399 were from the 7 rural hospitals. Table 5.1 outlines the number of isolates per hospital by MRSA classification. The majority of isolates, ranging from 69 -100%, from the outreach hospitals were classified as community associated. This was in contrast to the OSUMC where only 26% were classified as community associated. Isolates were predominately skin and soft tissue specimens in both rural hospitals as well as OSU, 81% and 45%. The vast majority of skin and soft tissue isolates from the 7 rural hospitals were community associated cases (89%). Demographically, the combined patients were 54% male, 82% white, and had a median age of 50. They also were comprised of 13% blood isolates, 17% sputum, and 59% skin and soft tissue isolates. A majority of isolates, 49%, were community associated, while 28% and 22% were hospital acquired and hospital acquired community onset. Only 17% of all isolates had a previous history of MRSA and only 20% had a history of placement if an invasive device. Table 5.2 highlights the descriptive statistics and comparisons of categorical data between CA MRSA and HA MRSA patients for the 7 rural OSHN members, and table 5.5 highlights the same for the OSUMC. The mean age for all OSHN patients was 48.3 years, however when broken down into CA MRSA versus HA MRSA, the mean age for CA MRSA patients was 44 while 73 for HA MRSA
patients. This gave a corresponding t-test p-value < 0.001. Table 5.3 describes the overall statistics of continuous variables for the OSHN hospitals, while table 5.4 examines the comparison of continuous variables between CA MRSA and HA MRSA for patients from the OSHN. The difference in mean age was also observed at the OSUMC, where the overall mean was 52, and the CA MRSA mean was 42 with the HA MRSA mean being 55. Table 5.6 describes the overall statistics of continuous variables for the OSUMC, while table 5.7 examines the comparison of continuous variables between CA MRSA and HA MRSA for patients from the OSUMC.

5.3.2 Proportion of CA MRSA in rural hospitals

Out of the total of 399 MRSA isolates from the rural outreach hospitals, 339 or 85% were classified as community onset. In contrast, the validation dataset from the OSUMC had a total of 26% CA MRSA cases. A chi square test of proportions showed a significant p-value of < 0.0001.

5.3.3 Model building process

The data collection form included 270 total variables. Running a model with all these variables was not practical. Therefore only those variables that were biologically plausible and clinically associated were chosen to be included in the model building process. This set was reduced to 17 variables: age, alcohol use, presence of lung disease, gender, history of past surgeries, presence of diabetes, creatinine level, hematocrit level, hemoglobin level, RBC level, presence of a fever, history of past trauma, neoplasms, history of renal failure, tobacco use, drug use and race. The first step in the model building process was to run each variable in a univariate model with CA MRSA status being the outcome. Drug use and race were dropped since they predicted the data
perfectly. Table 8 details each variable, and whether or not it was added to the main effects model building process. Of the 17 total variables 13 were found to be significant at the chi square p-value of 0.2. This less conservative cutoff was used in order to make sure no potentially significant variables were left out. Age was found to be the variable with the highest chi square statistic and therefore the lowest p-value (p < 0.001). Thus it was added to the main effects model first.

Using forward selection, each variable was added to the model with CA MRSA and age. No new variables were significant at the 0.05 alpha level. Thus the model building process was concluded in two steps with the final model comprising of only the variable age.

The continuous variable of age was then tested for the assumption of linearity in the logit. Since the model was essentially a univariate model, a smooth scatter plot was graphed. The plot was linear and therefore the assumption of linearity in the logit held and the final model was accepted.

5.3.4 Diagnostic statistics

Diagnostic tests including leverage, change in deviance, and influence were examined next. The graphs of the predictive values against the change in chi square values, deviance, and beta values were plotted. No outlying observations were noted.

5.3.5 Calibration and discrimination

Calibration of the model building dataset was determined first. The Hosmer-Lemeshow Goodness-of-Fit test obtained a chi square value of 3.45 with 8 degrees of freedom, corresponding to a p-value of 0.90. Thus the predicted values are indeed a good representative of the observed values. Discrimination of the model by using the area
under the curve of the graph of the sensitivity versus one minus the specificity was found to be 86%. This is interpreted as an excellent amount of discrimination.

5.3.6 Validation

The final model predicted by using the model building dataset (OSHN hospitals) was then assessed for validation by applying it to the predetermined validation set (OSUMC), and running the Hosmer-Lemeshow Goodness-of-Fit test on it. A chi square value of 9.31 with 10 groups and 8 degrees of freedom, corresponding to a p-value of 0.32 was obtained. This signifies that the model built is valid. However, the discrimination decreased to 52%.

5.4 Discussion

The goal of this study was to estimate the proportion of community associated MRSA cases among all MRSA cases from multiple rural hospitals and examine the risk factors associated with community acquired MRSA. The proportion of CA MRSA from all MRSA isolates in the 7 rural OSHN hospitals was 85%. This was in contrast to the proportion of CA MRSA at the OSUMC, which was only 26%. This finding is extremely important as it gives weight to the concept that community associated MRSA cases in recent years have increased in number and overall proportion of isolated MRSA cases. It also gives validity to the notion that CA MRSA seems to be replacing traditional healthcare associated MRSA as the predominant strain (Popovich et al., 2008).

MRSA is regarded as the most common healthcare-associated infection (HAI) (Chambers, 2001) and thus has been the focus of countless campaigns and prevention strategies due to its high mortality and morbidity rate. Over the years these prevention
strategies have seemed to work as the number of HA cases have gone down. This would seem true in our sample for the rural hospitals but not for the OSUMC, a large academic medical center. It is therefore important to look at the inherent differences between these two types of hospitals. The rural hospitals are smaller and often have a core group of individuals who are responsible for multiple areas in the hospital, for example an IP may be in charge of infection control as well as patient safety and employee health. When one individual is able to oversee a multitude of polices and areas of the hospital it creates a greater sense of cooperation with the hospital. The smaller hospitals are therefore able to tackle the issues of hospital acquired infections. Making sure that proper hand hygiene and contact isolation guidelines are in place. The large academic medical center on the other hand may in fact have issues trying to put all of these needed policies into a smooth action plan. There will be more people involved and a larger area to cover, thus creating the chances that certain areas will be missed. The number of patients seen is also extremely different. The roughly 1200 bed academic medical center certainly sees more patients in number and severity than the smaller hospitals do.

Community acquired MRSA infections occur in populations that do not have a known healthcare related exposure. The goal of this study was to examine the risk factors associated with community acquired MRSA. The main finding was that only age was found to be a significant risk factor for CA MRSA. The odds ratio for age and CA MRSA was 0.92, thus older age has a slightly protective nature to it. This result is in line with several other studies that found that younger people are at higher odds of having CA MRSA than older people (Seybold et al., 2006; Forsblom et al., 2011).
The overall model validity of this study is good. An important aspect of model validity in this study was having the assumption of the linearity of the logit hold. Good model validity is also proven by the excellent discrimination value of 86%, and by the non-significant p-value of the Hosmer-Lemeshow chi square statistic.

A major limitation of this study was the use of retrospective hospital records as the main source of patient information. This poses several issues the first of which is the accuracy of hospital medical records. The 8 participating hospitals had a variety of ways to capture data. Several of them used paper charts while 5 of them had some form of electronic charting. Although none of them had completely adopted electronic charting, and not all information was obtainable in either the paper or electronic based chart. Therefore some variables had missing data and were not able to be included into the analysis. The quality of medical documentation will also vary from hospital to hospital. Also, because many of the OSHN member hospitals patients were outpatient or emergency patients certain data was not available such as visit history or previous MRSA exposure. Using retrospective hospital and medical records data poses several challenges to obtaining complete information.

5.5 Conclusions

MRSA is a hardy and extremely virulent multidrug resistant organism that has been a major cause of hospital acquired infections ever since its discovery in the 1960’s. It has severe consequences such as causing increased morbidity, hospital length of stay, economic burden, and mortality. It has been the focus of numerous prevention strategies by a multitude of national organizations. Recently, as prevention strategies for hospital acquired MRSA take hold and the rate of hospital acquired MRSA begins to decline, the
rate of community associated MRSA has increased. This is an alarming and poorly understood trend, as these are infections in populations that have no known healthcare exposure or risk factor. This study found that only age was a significant risk factor in terms of community MRSA. It is important that further research is done to understand the risk factors and links associated with community associated MRSA so that new and novel prevention strategies, using existing resources and cutting edge technology, can be developed.
<table>
<thead>
<tr>
<th>Hospital</th>
<th># of isolates</th>
<th>CA MRSA</th>
<th>% of CA MRSA cases</th>
<th>HA MRSA</th>
<th>% of HA MRSA cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSUMC</td>
<td>625</td>
<td>164 (26%)</td>
<td>-</td>
<td>461 (74%)</td>
<td>-</td>
</tr>
<tr>
<td>Outreach 1</td>
<td>52</td>
<td>40 (77%)</td>
<td>12</td>
<td>12 (23%)</td>
<td>20</td>
</tr>
<tr>
<td>Outreach 2</td>
<td>16</td>
<td>14 (87%)</td>
<td>4</td>
<td>2 (13%)</td>
<td>3</td>
</tr>
<tr>
<td>Outreach 3</td>
<td>84</td>
<td>74 (88%)</td>
<td>22</td>
<td>10 (12%)</td>
<td>17</td>
</tr>
<tr>
<td>Outreach 4</td>
<td>81</td>
<td>72 (89%)</td>
<td>21</td>
<td>9 (11%)</td>
<td>15</td>
</tr>
<tr>
<td>Outreach 5</td>
<td>100</td>
<td>86 (86%)</td>
<td>25</td>
<td>14 (14%)</td>
<td>23</td>
</tr>
<tr>
<td>Outreach 6</td>
<td>24</td>
<td>24 (100%)</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Outreach 7</td>
<td>42</td>
<td>29 (69%)</td>
<td>9</td>
<td>13 (31%)</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 5.1. Number of isolates by Hospital with MRSA classification

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>CA MRSA</th>
<th>HA MRSA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen Type</td>
<td>Total</td>
<td>CA MRSA</td>
<td>HA MRSA</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>8 (2%)</td>
<td>3 (1%)</td>
<td>5 (9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>325 (81%)</td>
<td>302 (89%)</td>
<td>23 (38%)</td>
<td></td>
</tr>
<tr>
<td>Sputum</td>
<td>37 (9%)</td>
<td>20 (6%)</td>
<td>17 (28%)</td>
<td></td>
</tr>
<tr>
<td>Stool</td>
<td>2 (1%)</td>
<td>1 (0%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>23 (6%)</td>
<td>12 (4%)</td>
<td>11 (18%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (1%)</td>
<td>1 (0%)</td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>192 (48%)</td>
<td>169 (50%)</td>
<td>23 (38%)</td>
<td>0.09</td>
</tr>
<tr>
<td>White</td>
<td>391 (98%)</td>
<td>331 (98%)</td>
<td>60 (100%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Fever</td>
<td>59 (20%)</td>
<td>41 (12%)</td>
<td>18 (30%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Past Trauma</td>
<td>7 (2%)</td>
<td>5 (1%)</td>
<td>2 (3%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Past surgery</td>
<td>58 (15%)</td>
<td>40 (12%)</td>
<td>18 (30%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal failure</td>
<td>15 (4%)</td>
<td>6 (2%)</td>
<td>9 (15%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>12 (3%)</td>
<td>5 (1%)</td>
<td>7 (12%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>62 (16%)</td>
<td>45 (13%)</td>
<td>17 (28%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Lung Disease</td>
<td>32 (8%)</td>
<td>25 (7%)</td>
<td>7 (12%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Drug use</td>
<td>9 (2%)</td>
<td>9 (3%)</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>121 (30%)</td>
<td>114 (34%)</td>
<td>7 (12%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>351 (88%)</td>
<td>293 (86%)</td>
<td>58 (97%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 5.2. Descriptive statistics and comparison of categorical variables between CA MRSA and HA MRSA patients for OSHN hospitals
<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Median</th>
<th>SE</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>48.3</td>
<td>46</td>
<td>1.07</td>
<td>18</td>
<td>94</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.32</td>
<td>1</td>
<td>.09</td>
<td>.3</td>
<td>8.0</td>
</tr>
<tr>
<td>hematocrit</td>
<td>37.0</td>
<td>37.1</td>
<td>.53</td>
<td>12.6</td>
<td>54.7</td>
</tr>
<tr>
<td>hemoglobin</td>
<td>12.5</td>
<td>12.6</td>
<td>.17</td>
<td>8.4</td>
<td>17.4</td>
</tr>
<tr>
<td>RBC</td>
<td>4.19</td>
<td>4.1</td>
<td>.05</td>
<td>2.7</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Table 5.3. Descriptive statistics of continuous variables for OSHN hospitals

<table>
<thead>
<tr>
<th>Variable</th>
<th>CA MRSA</th>
<th>HA MRSA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>44</td>
<td>73</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.19</td>
<td>1.59</td>
<td>0.038</td>
</tr>
<tr>
<td>hematocrit</td>
<td>37.94</td>
<td>34.5</td>
<td>0.004</td>
</tr>
<tr>
<td>hemoglobin</td>
<td>12.9</td>
<td>11.64</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RBC</td>
<td>4.3</td>
<td>3.91</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table 5.4. Descriptive statistics and comparison of continuous variables between CA MRSA and A MRSA patients for OSHN hospitals
### Table 5.5. Descriptive statistics and comparison of categorical variables between CA MRSA and HA MRSA patients for the OSUMC

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>CA MRSA  (n=164)</th>
<th>HA MRSA  (n=461)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>128 (21%)</td>
<td>14 (9%)</td>
<td>114 (25%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>282 (45%)</td>
<td>124 (76%)</td>
<td>158 (34%)</td>
<td></td>
</tr>
<tr>
<td>Sputum</td>
<td>140 (22%)</td>
<td>11 (7%)</td>
<td>129 (28%)</td>
<td></td>
</tr>
<tr>
<td>Stool</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>54 (9%)</td>
<td>10 (6%)</td>
<td>44 (10%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>21 (3%)</td>
<td>5 (3%)</td>
<td>16 (3%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>360 (58%)</td>
<td>92 (56%)</td>
<td>268 (58%)</td>
<td>0.65</td>
</tr>
<tr>
<td>White</td>
<td>449 (72%)</td>
<td>11 (68%)</td>
<td>338 (73%)</td>
<td>.16</td>
</tr>
<tr>
<td>Fever</td>
<td>193 (33%)</td>
<td>38 (23%)</td>
<td>155 (36%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Past Trauma</td>
<td>45 (7%)</td>
<td>13 (8%)</td>
<td>32 (7%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Past surgery</td>
<td>394 (64%)</td>
<td>59 (36%)</td>
<td>335 (73%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Renal failure</td>
<td>85 (14%)</td>
<td>3 (2%)</td>
<td>82 (18%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>118 (19%)</td>
<td>7 (4%)</td>
<td>111 (24%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>174 (28%)</td>
<td>30 (18%)</td>
<td>144 (31%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lung Disease</td>
<td>136 (22%)</td>
<td>21 (13%)</td>
<td>115 (25%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Drug use</td>
<td>41 (7%)</td>
<td>21 (13%)</td>
<td>20 (4%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>354 (57%)</td>
<td>98 (58%)</td>
<td>256 (56%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>184 (29%)</td>
<td>73 (44%)</td>
<td>111 (24%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 5.6. Descriptive statistics of continuous variables for the OSUMC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Median</th>
<th>SE</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>52</td>
<td>52</td>
<td>0.68</td>
<td>19</td>
<td>99</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.01</td>
<td>0.95</td>
<td>0.32</td>
<td>0.03</td>
<td>168</td>
</tr>
<tr>
<td>hematocrit</td>
<td>32.2</td>
<td>32</td>
<td>0.30</td>
<td>4.3</td>
<td>87.8</td>
</tr>
<tr>
<td>hemoglobin</td>
<td>11.2</td>
<td>10.9</td>
<td>0.19</td>
<td>4.9</td>
<td>99</td>
</tr>
<tr>
<td>RBC</td>
<td>3.95</td>
<td>3.63</td>
<td>0.09</td>
<td>1.69</td>
<td>20.6</td>
</tr>
</tbody>
</table>

Table 5.6. Descriptive statistics of continuous variables for the OSUMC
<table>
<thead>
<tr>
<th>Variable</th>
<th>CA MRSA</th>
<th>HA MRSA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>42</td>
<td>55</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.28</td>
<td>2.22</td>
<td>0.21</td>
</tr>
<tr>
<td>hematocrit</td>
<td>36.5</td>
<td>30.9</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>hemoglobin</td>
<td>12.3</td>
<td>10.9</td>
<td>0.002</td>
</tr>
<tr>
<td>RBC</td>
<td>4.4</td>
<td>3.82</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Table 5.7. Descriptive statistics and comparison of continuous variables between CA MRSA and A MRSA patients for the OSUMC

<table>
<thead>
<tr>
<th>Variable</th>
<th>df</th>
<th>Likelihood ratio</th>
<th>P-value</th>
<th>Added to main effects model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td>101.09</td>
<td>&lt; 0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>1</td>
<td>6.53</td>
<td>0.04</td>
<td>Yes</td>
</tr>
<tr>
<td>Lung Disease</td>
<td>1</td>
<td>1.16</td>
<td>0.26</td>
<td>No</td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>2.74</td>
<td>0.10</td>
<td>Yes</td>
</tr>
<tr>
<td>Past surgery</td>
<td>1</td>
<td>1.48</td>
<td>0.19</td>
<td>Yes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>7.68</td>
<td>0.004</td>
<td>Yes</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1</td>
<td>4.05</td>
<td>0.06</td>
<td>Yes</td>
</tr>
<tr>
<td>hematocrit</td>
<td>1</td>
<td>8.3</td>
<td>0.006</td>
<td>Yes</td>
</tr>
<tr>
<td>hemoglobin</td>
<td>1</td>
<td>11.67</td>
<td>0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>RBC</td>
<td>1</td>
<td>9.75</td>
<td>0.003</td>
<td>Yes</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>11.28</td>
<td>&lt; 0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Past Trauma</td>
<td>1</td>
<td>0.85</td>
<td>0.33</td>
<td>No</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>1</td>
<td>12.4</td>
<td>&lt; 0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>1</td>
<td>16.83</td>
<td>&lt; 0.001</td>
<td>Yes</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>1</td>
<td>13.5</td>
<td>.001</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 5.8. Univariate models
Table 5.9. Final model parameter estimates and p-values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Df</th>
<th>Parameter estimate</th>
<th>SE</th>
<th>P-value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1</td>
<td>5.36</td>
<td>0.54</td>
<td>&lt; 0.001</td>
<td>4.3, 6.4</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>-0.07</td>
<td>0.008</td>
<td>&lt; 0.001</td>
<td>-0.08, -0.05</td>
</tr>
</tbody>
</table>

Table 5.10. Odds Ratios and 95% Confidence Intervals for final model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.92</td>
<td>0.90 – 0.94</td>
</tr>
</tbody>
</table>

Area under ROC curve = 0.8669

Figure 5.1. ROC curve
Chapter 6: Utilizing GIS and Social Networking Analysis to Understand the Clonal Variants and Transmission Patterns of MRSA

6.1 Introduction

Methicillin Resistant *Staphylococcus aureus* (MRSA) is a hardy and extremely virulent multidrug resistant organism that has been a major cause of hospital acquired infections ever since its discovery in the 1960’s. It has severe consequences such as causing increased hospital length of stay, economic burden, morbidity, and mortality (APIC, 2010). It has been the focus of countless campaigns and prevention strategies by a multitude of national organizations due to high mortality and morbidity rate. Recently, as prevention strategies for hospital acquired MRSA take hold and the rate of hospital acquired MRSA begins to decline, the rate of community associated MRSA has increased.

The chief mode of transmission of MRSA is by environmental contamination and from one person to another (patient to patient, patient to healthcare worker, and vice versa). The primary mode of transmission from person to person is via soiled hands. Several studies have proven that by merely correctly conducting hand hygiene, rates of infections have decreased. In one such study by Song et al., the authors sought to measure the impacts of hand hygiene compliance in a neonatal ICU by conducting monthly hand hygiene compliance audits before or after patient contact (Song et al., 2011). They
observed that proper hand hygiene compliance resulted in a 40% reduction of MRSA transmission, which translated into an avoidance of 79.4 extra days in the hospital and $215,000 per infected patient. Likewise proper cleaning of contaminated objects can also reduce the risk of transmission of MRSA (Boyce et al., 1997).

Transmission of MRSA from contaminated objects and person to person contact can cause both intra-facility as well as inter-facility transmission. It is therefore important to examine how and to what extent organisms are being transmitted from facility to facility. As MRSA transmission rates evolve, so does the organism itself (Sonneven et al., 2011). Clonal variants of the organism can be found in all settings and types of MRSA infections.

Newer technologies and novel techniques can enhance the understanding and breadth of MRSA clonal variants and transmission patterns. The purpose of this study was to identify and describe patterns of suspected intra-facility and inter-facility transmission of MRSA by evaluating epidemiological and geographic links by means of geographic information system and social network analysis.

6.2 Methods

6.2.1 IRB approval and funding

This study was conducted with the approval and under the supervision of the Institutional Review Board (IRB) at the Ohio State University Office of Responsible Research Practices (ORRP). The study was of minimal risk to the participants and therefore an expedited review and waiver of consent was requested and approved. Collected clinical MRSA positive isolates fall under IRB category 5; “Research involving materials (data, documents, records, or specimens) that have been collected or will be
collected solely for non-research purposes (such as medical treatment or diagnosis)” (OSU ORRP, 2010). Collaborating hospitals without their own IRB were asked to defer approval and oversight of the study to The Ohio State University IRB. All research staff, including those at collaborating facilities, completed basic IRB and HIPAA training by enrolling in the online Collaborative IRB Training Initiative (CITI) courses. A memorandum of understanding (MOU) was signed by the researchers and the hospitals detailing interactions, data sharing agreements, and other legal matters. A standard operating procedure (SOP) detailing the roles and responsibilities of the OSUMC, the outreach hospitals, and the OSU IRB was drafted and signed by participating hospitals to ensure the ethical and moral conduction of research, and the safety of patients. Funding for this study was provided by the Center for Disease Control and Prevention (CDC) Epicenter’s program (cooperative agreement CI000328).

6.2.2 Study setting

The study was conducted at the Ohio State University Medical Center (OSUMC) and 7 outreach hospitals collectively known as the Ohio State Health Network. A detailed description of the OSHN and these hospitals can be found in chapters 3 and 4.

6.2.3 Inclusion Criteria

Eligible participants included adult patients, defined as greater than or equal to 18 years, admitted to any of the OSUMC units including units in the University Hospital Main, OSU East Hospital, Ross Heart Hospital, and the James Cancer Hospital and/or OSHN hospitals during the study period who had a positive MRSA isolate. Out patients, including emergency room admissions, at the OSHN hospitals were also included. The
data collection for this study occurred over a one year time period (March 2009 – March 2010).

6.2.4 Exclusion Criteria

Patients who did not have a positive MRSA culture and/or were younger than 18 years of age were excluded from the study. Due to IRB restrictions, prisoners were also excluded.

6.2.5 Data collection process

Data collection for this study occurred at three distinct levels and locations. The first level was at the local hospital. The infection preventionist at each OSHN hospital was responsible for data collection and entry. Due to the high number of cases from OSUMC a team of physicians and infection preventionists (IP) filled out the data collection form. To ensure quality and the same standard of collection, a data dictionary was developed explaining each data field. The second level of data collection occurred via the microbiology lab. The OSUMC microbiology lab conducted genotypical and molecular analysis on all (OSUMC and OSHN member hospitals) collected MRSA isolates. Samples were also sent to other labs for more detailed or confirmatory analysis, if and when needed. The last level of data collection occurred at the OSUMC IW where system analysts collated identified geospatial data and performed geographical information systems analysis.

The data collection process took place in eight steps. A detailed methodology of the data collection has been described in chapters 3 and 5. Here we focus on the methods for the genotypical analysis and sampling plan for acquiring isolates at both OSUMC and the OSHN member hospitals. Figure 6.1 depicts the detailed data collection process.
6.2.6 Molecular techniques

The genotypical testing of the collected MRSA isolates and their subsequent classification into clonal clusters was achieved by means of rep-PCR testing.

Rep-PCR testing was completed by using the DiversiLab Microbial Typing System by Bacterial Barcodes, Inc. This system, developed in 2005, is a standardized and automated method of conducting rep-PCR DNA fingerprinting. The developers modified the lengthy and complex manual process by modifications of “rep-PCR chemistry and thermal cycling parameters, incorporation of microfluidics-based DNA
amplicon fractionation and detection, and internet-based computer-assisted analysis, reporting, and data storage” (Healy et al., 2005). The system has been commercially available for the past several years.

All rep-PCR typing was conducted by the OSUMC microbiology laboratory’s trained technicians. The first step in this process was to extract the DNA from the collected MRSA isolates. After DNA extraction, rep-PCR primers were then used. These primers target and bind to multiple noncoding, repetitive sequences interspersed throughout the bacterial genome. Samples were then amplified using the DiversiLab Kit for DNA fingerprinting (Bacterial Barcodes, Inc. Athens, GA). The kit contained an instruction guide, which was precisely followed by the OSU technicians. The automated DiversiLab System then detected the rep-PCR products and analyzed the virtual gel image creating a dendrogram. The software analyzed the electropherogram results of each individual isolate and compared the percentage of DNA similarity by comparing locations and intensities of individual peaks of one isolate to another isolate. Resulting bands illustrated the similarities between isolates. Isolates were clustered together by the software if there are 0-2 band differences. If there were 3 or more band differences, the isolate was classified as a separate cluster. The DiversiLab System software also included a genotype library where rep-PCR typed isolates were matched to a reference library of other genotypical and molecular typing methods such as PFGE and SCCmec typing.

6.2.7 Honest broker

In 2006, the OSU IRB recognized the OSUMC IW as an essential stakeholder and keeper of healthcare related data and thus designated them as an “honest broker.” The honest broker status allows the IW to “provide an OSU IRB approved process” and gives
researchers and administrators either coded or de-identified data without prior IRB approval for non-human subjects or exempt research (Lie et al., 2009). It also allows for the research study collection and storage of identifiable data on OSUMC IW servers and databases. The OSUMC IW acts as the keeper of identifiable data and transmits only de-identified data to researchers.

The honest broker status is an essential component of this study. By invoking this status, the OSUMC IW took full responsibility to store all identifiable specimen information from OSHN member organizations and transmit them for analysis in the form of a limited data set with the HIPAA-defined PHI removed and no link back to patient identifiers. As keepers of the identifiable data the OSUMC IW still maintained and kept full dates, ages, and addresses with zip codes in their secure databases. Since they are an honest broker any geographical maps generated were created by them. This allowed for the collection of geospatial data i.e. patient addresses while preserving patient confidentiality and privacy issues and being HIPAA compliant.

6.2.8 Geographical Information Systems

Geographical Information Systems (GIS) is defined as a system designed to capture, store, manipulate, analyze, manage and present all types of geographically referenced data (Foote and Lynch, 2000). For many years it has been used in population and environmental studies (Peuquet and Marble, 1990). In recent years, studies have been published examining and employing the use of GIS software to track outbreaks and/or transmission of hospital acquired infections (Lee and Wong, 2010).

Data collected as part of this study included address of the patient at the time the specimen was collected. As this is a HIPAA defined patient identifier the geocoding and
generation of maps was completed via the honest broker i.e. the OSUMC IW. Analysts in the OSUMC IW used the ESRI ArcGIS software suite to geocode all isolates in the stored MRSA research Oracle database tables, located on the IW servers. Address and clinical isolate information, such as rep-PCR type, PFGE type and infection site, were first extracted to an Excel spreadsheet and then imported, by using the ArcCatalog software, into a geodatabase table from which the addresses were geocoded. Geocoding was based on the U.S. Nationwide Streets address locator available from within ArcMap, a component and additional software in the ArcGIS package.

Maps and spatial data were generated by layering the shapefiles for the state, counties, zip codes and census tracts with the geocoded MRSA address data. Basic point maps differentiating the hospital with which the isolate was associated, as well as either the rep-PCR type or the infection site (e.g. blood, skin and soft tissue, sputum) by the use of different symbols and colors were generated. Graduated color maps were also developed to represent varying concentrations of isolates at both a county and a zip code level. Census tract data was subsequently loaded back into the MRSA research database table for further analysis.

6.2.9 Social Networking Analysis

6.2.9i Introduction to Social Networking Analysis

Orgnet, a social networking research firm, has defined social network analysis (SNA) as the mapping and measuring of relationships and flows between people, groups, organizations, computers or other information/knowledge processing entities (Orgnet, 2010). SNA allows for both a visual and computational analysis of how relationships and outcomes are linked to each other. According to Hanneman and Riddle in their textbook
Introduction to Social Network Analysis (Hanneman and Riddle, 2005), SNA is the analysis of individuals and their relationship to each other. This is opposite to conventional and survey data analysis, which examines individuals and their attributes. In SNA, the individuals are known as actors depicted as nodes who exhibit relationships or ties with each other. Another key difference between SNA and conventional or survey analysis is the concept and understanding of independence. Since in SNA, researchers are looking for relationships, the actors are not independently sampled. They are in fact chosen due to some known linkage between the actors, often being some naturally occurring boundary such as a zip code, neighborhood, or school. Thus SNA does not use sample populations, but instead uses censuses. To this date, there are no known methods for approximations of sampling distribution in SNA. Crouch and Wasserman in their “Practical guide to fitting p* Social Network Model via Logistic regression” note that because the assumption of independence in SNA models is not entirely valid, measures of likelihood statistics cannot carry a strict statistical interpretation. They can, however, be used as “a guide for evaluating model fitness” (Crouch and Wasserman M, 1997).

Social Network analysis has been used in the research of sexually transmitted diseases and tuberculosis infection to identify unrecognized patterns of transmission. By mapping out and visualizing epidemiological and demographic contact information data for each case and their contacts, connections between cases can be identified (Gardy et al., 2011). Application of this method to MRSA investigations can identify common links in health-care associated networks (e.g. hemodialysis unit, same outpatient clinic, common healthcare worker with MRSA colonization). Identification of new and unique transmission dynamics can and will consequently improve MRSA infection control.
guidelines and programs by detailing specific links and actors in the transmission process.

6.2.9ii Sampling of MRSA isolates

All adult MRSA positive isolates from the seven OSHN outreach hospitals were sampled.

The OSUMC averages approximately 1500 positive MRSA isolates each year. Collecting and genotyping all of these isolates was not feasible due to budget, time, and personnel restraints. Thus a random sample with the sampling frame being all MRSA positive isolates was used.

Due to the dependent nature of subjects in social networking analysis, it was important to collect isolates that are geographically and possibly socially linked to the other OSHN hospitals. In order to achieve this OSUMC isolates were separated into two categories. The first category was those isolates that are targeted from the same zip codes as the catchment areas of the OSHN hospitals, while the second were OSUMC MRSA isolates from the non-targeted zip code. A list was obtained from each of the OSHN hospitals detailing the zip codes of their patient catchment areas.

The OSUMC IW created a query that first identified all the finalized daily positive MRSA cultures for admitted adults at the OSUMC. The query pulled the patient’s name, medical record number as well as full address with zip code. The query then automatically matched to the list of targeted zip codes. This query subsequently generated two lists. The first list was those patients in targeted zip codes while the second was those in non-targeted zip codes. The list was generated twice a week. Appendixes G
and H, designed by the OSU research team, give the detailed instructions for generating both lists.

A key factor to social networking analysis is choosing (Hanneman and Riddle, 2005) subjects that are linked to each other. Due to this factor, all positive MSRA isolates in the targeted zip codes were sampled. This was achieved by the researcher taking the IW targeted list and first comparing it to a running line list of all previous patients to ensure that no duplicates were sampled. The isolates from the targeted zip codes were noted and the microbiology laboratory was notified to retain those isolates and begin rep-PCR testing on them.

In the case of the non-targeted zip codes, a random sample was taken. Researchers at OSU took the IW non-targeted zip code list and compared it to a running line list of all previous patients to ensure that no duplicates were sampled. Based on the available budget, it was estimated that rep-PCR analysis could be performed on approximately 13 non-targeted zip code patients each week. From the list of non-targeted zip codes 13 patients were randomly selected. In order to randomly select patients, each patient on the list was given a number and then a random generator was used to select 13 numbers from the amount of isolates. The chosen isolates from the non-targeted zip codes were noted and the microbiology laboratory was notified to retain those isolates and begin rep-PCR testing on them.

6.2.9iii Social networking software and analysis

Using identified MRSA clusters from the molecular genotyping and from the GIS generated maps, specific clusters that appear to be linked to each other were chosen and further analyzed by means of social networking analysis. The criterion for choosing the
clusters was a combination of number of isolates in the cluster, geographical location, PFGE type, and other interesting or relational variables. Data collected from OSUMC was linked to the rural OSHN hospitals by either targeted zip code and/or previous admissions in multiple participating hospitals. This fulfilled the criteria for SNA that data must be linked and not independent of each other. The social networking software UNICET was used for the analyses. The software was developed by Steve Borgatti, Martin Everett and Lin Freeman and is distributed by Analytic Technologies. The freeware program NETDRAW which helps draw networks comes with UCINET (UCINET, ND, http://www.analytictech.com/ucinet). UCINET and NETDRAW examine the data for any social or demographic links between the patients and graph them accordingly. Generated graphs depict a node and its subsequent ties to other nodes.

6.3 Results
6.3.1 MRSA Isolates and clusters

Over a year time period, from March 2009 to March 2010, a total of 1024 MRSA isolates were collected. Rep-PCR analysis was performed on all isolates. Among the 1024, 625 were from the OSUMC while 399 were from the 7 outreach hospitals. Overall these 1024 isolates consisted of 75 unique rep-PCR patterns, and were geographically distributed in 431 census tracts and 243 zip codes. Table 6.1 outlines the number of isolates, rep-PCR patterns, zip codes and census tracts by hospital. The number of isolates clustered within a rep-PCR pattern group ranged from 27 patterns with only one isolate to a maximum of 178 isolates associated with a pattern. Table 6.2 outlines the specific patterns and the frequencies associated with each one. Seven rep-PCR patterns (9, 63, 2, 12, 60, 66, and 7) accounted for 64% of all rep-PCR types. The rep-PCR
patterns also accounted for 10 different PFGE classes and included several that were not matched to a class in the DiversiLab Microbial Typing System database. The majority of isolates were either USA100 or USA300, (N=31 or 41% and N=16 or 21%). Table 6.3 details the specific rep-PCR patterns and their corresponding PFGE and SCCmec classes. Demographically these isolates were 54% male, 82% white, and had a median age of 50. They also comprised of 13% blood isolates, 17% sputum, and 59% skin and soft tissue isolates. A majority of isolates, 49%, were community associated, while 28% and 22% were hospital acquired and hospital acquired community onset. Only 17% of all isolates had a previous history of MRSA and only 20% had a history of placement of an invasive device. Table 6.4 outlines demographic and patient characteristics of all patients by hospital.

6.3.2 GIS

The OSUMC IW, under the auspices of the honest broker policy, successfully mapped all collected MRSA isolates by means of ArcGIS. The registered address at time of admission was used for the mapping. Maps depicting the number and types of isolate were generated for each OSHN member hospital as well as a general map of Ohio depicting cataloged cases (Figures 6.2 – 6.13). The generated maps added insight and information to the types of specimens and encatchment areas of the hospitals. The maps successfully revealed the geographical spread of clusters.

6.3.3 SNA

Rep-PCR genotyping analysis clustered the isolates into 75 distinct patterns. Several clusters, such as pattern 63 and 9, were fairly similar to each other but still had enough difference in bands that they were deemed as separate clusters. These clusters
were so widely spread among the communities and without any discernible transmission pattern that it was hypothesized that these patterns may in fact be the common endemic strain of MRSA. Each of the patterns was further examined for any possible links of intra and/or inter-facility transmission. Transmission links included admission to same hospital, history of admission to an OHSN member hospital, close proximity of admission and specimen dates, unit and/or room. The medical record was also reviewed for any additional insights that might give rise to transmission links or patterns between patients. The social networking software UCINET was used to examine and generate graphical representations of the potential link between patients. We describe the results from 2 clusters, patterns 29 and 101, which exhibit potential links of both intra and inter facility transmission here.

Cluster 29 comprised isolates from 8 patients. The isolates of 6 patients were collected at 4 of the 7 participating OSHN member hospitals, while only 2 isolates were collected at the OSUMC. Demographically these isolates were 50% male, 88% white, and had a median age of 72.5. They also comprised of 25% blood, 38% sputum, and 25% skin and soft tissue isolates. A majority of isolates, 50%, were hospital acquired community onset cases, while 25% and 25% were community associated and hospital acquired. Only 25% of the patients from whom isolates were obtained had both a previous history of MRSA and a history of placement of an invasive device. Table 6.5 outlines demographic and patient characteristics of all patients by hospital for cluster 29.

The first cataloged case of this rep-PCR pattern was from hospital 4 in March 2009. The patient came from a nursing home and was seen as an outpatient via the emergency room. Since this patient was seen in the emergency room as an outpatient
their hospital medical record was sparse in terms of details regarding previous hospital stays both in house as well as externally. The second reported case of rep-PCR pattern 29 comes from hospital 3 in the first week of April, 2009. This patient was admitted from their residing nursing facility. A week after discharge another case (patient #5) was reported at hospital 3 via a patient being admitted from the same nursing home as patient #2. Both these cases were classified as hospital acquired. Patient 3 was seen at the OSUMC also in the first week of April 2009. Patient 4 was admitted at hospital 1 in the first week of April but had been at the OSUMC in the month of February 2009. Patient 6 was isolated with the pattern 29 at hospital 1 roughly 1 week after patient 4. The 2 patients’ admission dates did cross over. Patient 7 was diagnosed in June 2009, at hospital 5 but had had several previous admissions in the past 12 months at the OSUMC. Finally, patient 8 was diagnosed at the OSUMC in October 2009. Although none of the admitted OSUMC patients nor the patients from OSHN hospitals who had a previous admission at the OSUMC were ever in the same ward/room or time frame, each patient did have the common factor of working with the physical therapy/rehabilitation team.

Figure 6.14 depicts the SNA analysis via UCINET.

Cluster 101 consisted of isolates from 7 patients. All isolates were collected at the OSUMC. Demographically these isolates were 71% male, 43% white, and had a median age of 51. They also comprised of 0 blood isolates, 43% sputum, and 43% skin and soft tissue isolates. A majority of isolates, 71%, were hospital acquired, while 0 and 29% were community associated and hospital acquired community onset. None of the isolates had a previous history of MRSA and 29% had a history of placement of an invasive
device. Table 6.6 outlines demographic and patient characteristics of all patients by hospital for cluster 101.

The 7 isolates from rep-PCR cluster 101 were found in 4 units and/or rooms of the OSUMC. The first cataloged case of this rep-PCR pattern was diagnosed in late October 2009. The patient was transferred from an outside hospital and housed in unit 1. Approximately 4 months after the patient was admitted, another patient (patient 6) was found to have the same rep-PCR pattern. Patient 6 was admitted into the same unit as patient 1, and housed 2 rooms down. Patients 2 and 4 were admitted approximately 13 days apart from each other with an overlapping stay. Both patients were transferred in and out of several hospital rooms during their stay, but were housed in the same room 1 week apart from each other. Both these patients were discharged to a nursing home in the same census tract and were also previously admitted to the OSUMC. Information in regards to the nursing home was not available. Patient 3 was diagnosed at the end of November 2009 and was the only isolate found in unit 2. A further review of the patient’s chart did not yield any additional information to a potential transmission pattern. Interestingly, patients 5 and 7 were admitted into the same room approximately 2 weeks apart from each other. Figure 6.15 depicts the SNA analysis via UCINET.

6.4 Discussion

The purpose of this study was to collect MRSA isolates from a wide geographical area, the OSUMC and 7 rural outreach hospitals, classify them into genotypical clusters, and describe patterns of suspected intra-facility and inter-facility transmission of MRSA. This was achieved by conducting molecular genotyping analysis, via rep-PCR testing, of all collected MRSA isolates, and then using geographic information system and social
network analysis based on collected epidemiological and social data to ascertain if specific transmission patterns of certain MRSA clusters existed. Seventy-five distinct MRSA clonal patterns, with 48 patterns having 2 or more isolates thus having the potential for cross transmission, were identified. Our study results show that MRSA does not exist as a single genetic entity, but is an ever evolving bacterium that has morphed, and continues to do so, from possibly a single original strain into many similar but genetically distinct clones.

The use of GIS proves to be a powerful tool and allows for the visualization of the spread of isolates across a large geographical area. It also meaningfully depicts which type of infections are occurring in which settings, such as skin and soft tissue infections occurring more in the rural settings and blood infections occurring at the urban academic medical center. The use of GIS is a formidable tool to the understanding of the extent of MRSA infections.

The two clusters highlighted in this analysis show a potential transmission pattern both within hospitals as well as between hospitals, and give us an insight as to the potential sources of MRSA infection that need to be looked at more carefully. Cluster 29 contained a total of 8 isolates, 2 of which were directly isolated at the OSUMC. However an additional 2 patients, whose MRSA strains were isolated at 2 different OSHN member hospitals, had a history of being a patient at the OSUMC a couple of months prior to their diagnosis. These patients, although not housed in the same units/rooms, did have the common factor of working with the physical therapy/rehabilitation team. Therefore it is plausible that either members of the physical therapy/rehabilitation team or objects used by them may be the source of contamination between patients. This seems logical as this
is a team of individuals who on a daily basis see numerous patients in multiple areas of a hospital. It is also important to note that 2 patients from hospital 3 were admitted via the same nursing home. Nursing homes have been a concern for public health officials and have been known to have MRSA issues (Reynolds C et al., 2011). Cluster 101, gives very good insight to the possibility of inter-facility transmission. It is important to note that for the 7 isolates only 4 units/rooms were noted, thus several isolates were isolated either in the same unit or room as another. Two sets of isolates were found several weeks apart in the same unit. Within these units the beds of these patients were next door to each other. Likewise, 2 patients who were found to have the same genotypical isolate were housed in the same room 2 weeks apart. It is again very plausible to assume that these patients transmitted the bacteria to one another by means of contaminated objects or healthcare workers.

These results highlight the importance of conducting proper hand hygiene and adhering to the strict policies of contact precautions. If healthcare workers properly wash their hands and potentially contaminated equipment is thoroughly cleaned, then the spread of MRSA via patients and foments can be limited and minimized.

There are several limitations to our study. Conventionally, SNA has been conducted by detailed face to face interviews with patients. We have attempted, to use hospital records as the main source of patient information as opposed to the patient themselves. This poses several issues the first of which is the accuracy of hospital medical records. The 8 participating hospitals had a variety of ways to capture data. Several of them used paper based charts while 5 of them had some form of electronic charting. Although none of them had completely electronic charting available, and not all
information was obtainable in either the paper or electronic based chart. The quality of medical documentation will also vary from hospital to hospital. Also because many of the OSHN member hospitals patients were outpatient or emergency patients certain data was not available such as visit history or previous MRSA exposure. Using retrospective hospital and medical records data poses several challenges to obtaining complete information.

The use of the honest broker status by the OSUMC IW did however prove to be advantageous and beneficial. By allowing the IW to act as an honest broker geographical information was obtainable. This allowed maps to be generated. These maps added depth into the understanding of which specimen types are common and to the general extent of MRSA in an encatchment area. It also gave insight into the spread of common and unique clonal strains of MRSA. Without the honest broker protocol collection of this data would not be possible.

6.5 Conclusion

MRSA is a hardy and extremely virulent multidrug resistant organism that has been a major cause of hospital acquired and community associated infections. It has severe consequences such as causing increased, hospital length of stay, economic burden, morbidity and mortality. The chief mode of transmission of MRSA is from one person to another (patient to patient, patient to healthcare worker, and vice versa) and by environmental contamination, such as a bed rail or patient room equipment. Novel methods using SNA and GIS can be employed to examine and gain an in-depth understanding of the transmission patterns of MRSA within and between hospitals across a regional geographical area, thus leading to better methods of prevention.
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Table 6.1. Frequency of isolates, rep-PCR patterns, census tract, and zip codes by hospital
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Table 6.3. Rep PCR patterns and corresponding PFGE and SCCmec types
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<td>15 (19%)</td>
<td>22 (22%)</td>
<td>7 (29%)</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>Hx MRSA</td>
<td>130 (21%)</td>
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<td>1 (6%)</td>
<td>10 (12%)</td>
<td>14 (18%)</td>
<td>16 (16%)</td>
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<td>3 (7%)</td>
</tr>
<tr>
<td>Hx invasive device</td>
<td>180 (29%)</td>
<td>0</td>
<td>2 (13%)</td>
<td>3 (4%)</td>
<td>6 (7%)</td>
<td>10 (10%)</td>
<td>1 (4%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>CA MRSA</td>
<td>164 (26%)</td>
<td>40 (77%)</td>
<td>14 (88%)</td>
<td>74 (88%)</td>
<td>72 (89%)</td>
<td>86 (86%)</td>
<td>24 (100%)</td>
<td>29 (69%)</td>
</tr>
<tr>
<td>HA MRSA</td>
<td>204 (32%)</td>
<td>5 (10%)</td>
<td>1 (6%)</td>
<td>5 (6%)</td>
<td>3 (4%)</td>
<td>2 (2%)</td>
<td>0</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>HACO MRSA</td>
<td>257 (41%)</td>
<td>7 (13%)</td>
<td>1 (6%)</td>
<td>5 (6%)</td>
<td>6 (7%)</td>
<td>12 (12%)</td>
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<td>8 (19%)</td>
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Table 6.5. Demographic and patient characteristics for rep-PCR pattern 29 by hospital

<table>
<thead>
<tr>
<th></th>
<th>N= 8</th>
<th>OSUMC</th>
<th>Hospital 1</th>
<th>Hospital 3</th>
<th>Hospital 4</th>
<th>Hospital 5</th>
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<tr>
<td>Female</td>
<td>4 (50%)</td>
<td>0</td>
<td>1 (50%)</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>7 (88%)</td>
<td>1 (50%)</td>
<td>2 (100%)</td>
<td>2 (100%)</td>
<td>1 (100%)</td>
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<tr>
<td>Age</td>
<td>72.5</td>
<td>49</td>
<td>68.5</td>
<td>80</td>
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<td>72</td>
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<td>Specimen Type</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>2 (25%)</td>
<td>1 (50%)</td>
<td>2 (100%)</td>
<td>0</td>
<td>0</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Sputum</td>
<td>3 (38%)</td>
<td>1 (50%)</td>
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<tr>
<td>SST</td>
<td>2 (25%)</td>
<td>0</td>
<td>0</td>
<td>1 (50%)</td>
<td>1 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Stool</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urine</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1 (12%)</td>
<td>0</td>
<td>0</td>
<td>1 (50%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>In patient</td>
<td>5 (63%)</td>
<td>2 (100%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>0</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Hx MRSA</td>
<td>2 (25%)</td>
<td>0</td>
<td>2 (100%)</td>
<td>0</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Hx invasive device</td>
<td>2 (25%)</td>
<td>1 (50%)</td>
<td>0</td>
<td>1 (50%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CA MRSA</td>
<td>2 (25%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HA MRSA</td>
<td>2 (25%)</td>
<td>0</td>
<td>0</td>
<td>2 (100%)</td>
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</tr>
<tr>
<td>HACO MRSA</td>
<td>4 (50%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>0</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td></td>
<td>N = 7</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>-------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2 (29%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>3 (43%)</td>
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</tr>
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</tr>
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<td>Specimen Type</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum</td>
<td>3 (43%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SST</td>
<td>3 (43%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>1 (14%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patient</td>
<td>4 (57%)</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hx MRSA</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx invasive device</td>
<td>2 (29%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA MRSA</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HA MRSA</td>
<td>5 (71%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HACO MRSA</td>
<td>2 (29%)</td>
<td></td>
<td></td>
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</tbody>
</table>

Table 6.6. Demographic and patient characteristics for rep-PCR pattern 101
Figure 6.2. Density Map of all MRSA cases
Figure 6.3. GIS Map of specimen types from all MRSA cases
Figure 6.4. GIS Map of all OSU cases
Figure 6.5. GIS map of hospital 1 cases
Figure 6.6. GIS map of hospital 2 cases
Figure 6.7. GIS map of hospital 3 cases

- Blood – 1 case
- Skin and soft tissue – 69 cases
- Sputum – 9 cases
- Urine – 3 cases
Figure 6.8. GIS map of hospital 4 cases

- **Blood** – 2 cases
- **Skin and soft tissue** – 68 cases
- **Sputum** – 2 cases
- **Urine** – 6 cases
Figure 6.9. GIS map of hospital 5 cases

- Blood – 4 cases
- Skin and soft tissue – 87 cases
- Sputum – 6 cases
- Urine – 3 cases
Figure 6.10. GIS map of hospital 6 cases

- Blood – 0 cases
- Skin and soft tissue – 20 cases
- Sputum – 2 cases
- Urine – 2 cases
Figure 6.11. GIS map of hospital 7 cases

- Blood – 0 cases
- Skin and soft tissue – 29 cases
- Sputum – 5 cases
- Urine – 7 cases
Ohio MRSA Cases
RepPCR Type 29
by Infection Type

8 Total Cases

Legend

- Blood - 2 Cases
- Other - 1 Case
- Skin and soft tissue - 2 Cases
- Sputum - 3 Cases

Figure 6.12 Rep-PCR 29
Ohio MRSA Cases
RepPCR Type 101
by Infection Type

7 Total Cases

Legend
△ Other - 1 Case
▲ Skin and soft tissue -2 Cases
▲ Sputum - 3 Cases
▲ Urine - 1 Case

Figure 6.13 Rep-PCR 101

Figure 6.14. SNA re PCR pattern 29
Timeline: October 2009 – February 2010

Figure 6.15. SNA re PCR pattern 101
Chapter 7: Strengths and limitations

7.1 Strengths

This study has several strengths. First of all, the existing infrastructure of both the OSHN and the OSUMC IW permitted for the easy leveraging of resources to develop and deploy the HIE. The existing expertise of the OSUMC Microbiology Laboratory in conducting rep-PCR analysis is another strength. This minimized the chances of typing and technique error. Another key strength was in the ability to engage the rural hospitals by utilizing the existing OSHN partnership, resources and setup. This led to the gaining of insight into the proportion, and risk factors of CA-MRSA while also learning about the intra and inter-facility transmission of MRSA. The ability to have captured all MRSA positive isolates from the entire population within these rural hospitals was also strength as it increased discriminatory power.

7.2 Limitations

This study has several limitations. First of all, reliance of obtaining isolates was on the microbiology laboratory of the OSHN hospitals. If a proper process is not in place, isolates may have been lost or not properly collected. Isolates may also not have been viable for rep-PCR testing if they were not cultured and shipped properly. Another limitation is the possibility of missing some MRSA cases. Some patients may be diagnosed with MRSA, but if no culture was taken then they will be missed. The
retrospective nature of the data collection also poses a problem. Misclassification of
patients into either HACO-MRSA or CA-MRSA could have also occurred if relevant
healthcare-associated risk factors were not available in the medical record or were not
collected by the researchers and if standardized definitions were not used. It is hoped that
this was kept at a minimum due to having a detailed data dictionary. Another key
limitation is based on our sampling plan for the validation set. In order to gain samples
for the SNA, patients must be linked to each other some way. This invalidates the
assumption of independence needed for logistic regression. This is a known issue with
SNA and to this date no statistical techniques have been derived to counter this issue.
Chapter 8: Conclusions

8.1 Conclusions

MRSA is a hardy and extremely virulent multidrug resistant organism that has been an increasing cause of hospital acquired infections ever since its discovery in the 1960’s. It has severe consequences such as causing increased morbidity, hospital length of stay, economic burden, and mortality. More recently, the epidemiology of MRSA has shifted so that CA-MRSA is an increasing threat both to the community-dwelling individuals and to hospitalized patients. This is an alarming and poorly understood trend, as these are infections in populations that have no known healthcare exposure or risk factor.

The chief mode of transmission of MRSA is from one person to another (patient to patient, patient to healthcare worker, and vice versa) and by environmental contamination. MRSA has been the focus of numerous prevention strategies by a multitude of national organizations.

The results of this study have important implications for a broad range of stakeholders including administrators, local and national policy makers, clinicians (including direct care providers and infection preventionists), and researchers across a range of disciplines. Using the findings of this research, these diverse stakeholders should continue to collaborate to find effective infection control strategies.
For administrators, we have demonstrated an effective, efficient, compliant means of sharing information about the epidemiology of MRSA. Collaboration between institutions – for example, academic medical centers and rural hospitals -- can bridge the knowledge and technology gap and provide a broader picture of how MRSA is spread within the community and in hospitals. Partnerships between rural and academic medical centers can stimulate development of best clinical practices by leveraging the strengths of both community hospitals and academic medical centers.

We have demonstrated that gaining trust and creating a framework of partnership between all stakeholders in collaborating organizations is critical to the success of any joint venture. In this study all OSHN member hospitals were eager to partner with OSU to increase their visibility and competitive edge by showing that they jointly were researching novel techniques for infection control and prevention. This results in a reputational advantage for community hospitals. In fact, several participating institutions published articles in their local newspaper highlighting the collaboration.

From an administrative perspective, implementation of the HIE was greatly facilitated by the use of the honest broker status which can serve as a model for further information sharing and collaboration. The honest broker status allowed for the collection and use of demographic, clinical, and geographic data because of the assurances provided by robust operating procedures.

We also demonstrated the importance of using information technology to facilitate collaboration. The use of HIT is no longer an anomaly but is in fact the norm and a necessity to safely, effectively, and efficiently treat patients. By utilizing and enhancing existing resources, protocols, and information technology infrastructure health
information exchanges can be developed. This will allow for the easy and safe transfer of healthcare information between hospitals. Novel techniques in health information technology and medical informatics such as the use of GIS and SNA can give rise to a deeper understanding of the transmission of infections agents and enhance control and prevention strategies.

In the past, the implementation of EHRs and HIT has been hindered by concerns about data security and privacy. Restrictions on access and safe guards need to be in place as to how much information is shared and by whom. The honest broker protocol is one way to permit sharing of data which open the possibility for expanded creating research consortiums across institutions and can serve as a model for information sharing by stakeholders in the wider community.

The sharing of a wide range of data through HIT using established protocols such as the HIE should be advocated and supported by policy makers and administrators. As shown in this study, the results of these collaborations can have specific, actionable implications for efforts to control MRSA in the hospital and the community.

For example, the results of this study on the prevalence of CA-MRSA can have implications for infection prevention activities. The finding that the proportion of CA MRSA in the 7 rural OSHN hospitals was 85% compared to 26% at OSU supports the finding that CA MRSA is replacing traditional healthcare associated MRSA as the predominant strain (Popovich et al., 2008). However, this study adds important information about the variation in CA MRSA in the hospital that occurs across geographic settings. This reinforces the notion that infection prevention strategies should
be targeted toward the epidemiology in a specific setting and that “one size fits all” approaches may not be the most effective.

When developing infection prevention strategies, it is therefore important to look at differences between two types of hospitals and design intervention strategies for that setting. For example, rural hospitals are smaller and often have a core group of individuals who are responsible for multiple areas in the hospital. An IP may be in charge of infection control as well as patient safety and employee health and thus may be able to tackle the issues of hospital acquired infections across departments more readily. On the other hand, a large academic medical center may have issues trying to put all of these needed policies into a smooth action plan. There will be more people involved and a larger area to cover, thus creating the chances that certain areas will be missed.

Understanding differences in organizational structure and MRSA epidemiology could result in a different set of control strategies between hospitals. In one setting, ensuring that proper hand hygiene and contact isolation guidelines are in place may be most important. In a hospital with a large proportion of CA MRSA, strategies could be designed to address introduction of community strains in to the hospital such as at entrances to the hospital and in the ER or emphasizing hand hygiene by visitors and patients.

Consistent with other research, we found that age was a significant risk factor for CA MRSA (OR 0.92) and that younger people are at higher odds of having CA MRSA than older people (Seybold et al., 2006; Forsblom et al., 2011). This may have implications for MRSA screening, isolation, and control policies. In contrast to most other medical conditions, we have found that it may be young, healthy, community-
dwelling individuals who are at highest risk of acquiring MRSA in rural settings and introducing these strains into the hospital.

However, we found that despite identifying and analyzing a large number of variables, risk factors for CA MRSA are relatively unknown and poorly understood. In order to fully address the impact of MRSA, more research is urgently needed. This study demonstrates three key areas of further research needs—application of molecular techniques to the epidemiology of MRSA, the ability of social networking analysis as a tool to understand MRSA transmission, and the feasibility of GIS as a way to identify trends in MRSA.

The results of the rep-PCR analysis show that MRSA does not exist as a single genetic entity, but is an ever-evolving bacterium that has morphed, and continues to do so, from possibly a single original strain into many similar but genetically distinct clones. The 1024 MRSA isolates comprised of 75 unique rep-PCR patterns, and were geographically distributed in 431 census tracts and 243 zip codes. The number of isolates clustered within a rep-PCR pattern ranged from 27 patterns with only one isolate to a maximum of 178 isolates associated with a pattern. Seven rep-PCR patterns (9, 63, 2, 12, 60, 66, and 7) accounted for 64% of all rep-PCR types, and probably represent the endemic strains of MRSA. The rep-PCR patterns also accounted for 10 different PFGE classes, 62% of which were either USA100 or USA300. Understanding the genetic differences of MRSA isolates allows us to examine which patterns may be more virulent -- cause more severe disease -- and the types of infections may be related to certain patterns. Further research and analysis needs to be done on these rep-PCR patterns to see
if prevention of transmission and infection control policies or strategies should be different based on genotype patterns.

Secondly, we have demonstrated that the use of GIS is a powerful tool that allows for the visualization of the spread of isolates across a large geographical area. It also meaningfully depicted which type of infections are occurring in which settings, such as skin and soft tissue infections occurring more in the rural settings and blood infections occurring at the urban academic medical center. The use of GIS is a formable tool to the understanding of the extent of MRSA infections and should be used in future applications. Research should address the best way to present GIS data in ways that can impact infection control practice and reduce the burden of MRSA.

Finally, we have shown that SNA can be a viable tool for understanding the links between transmission of MRSA cases. We used two specific examples of clusters to highlight the use of SNA to illustrate potential transmission patterns within a hospital as well as between hospitals. However, application of SNA in clinical practice will require further research in to the settings where SNA can be helpful in controlling disease and how clinicians might use this data to develop and implement prevention strategies.

This study provides a firm foundation for addressing the ongoing problem of MRSA in the community and hospital settings. By developing a partnership between community hospitals and an academic medical center, we have shown that collaboration on infection control and prevention studies can lead to important findings which have implications for infection prevention strategies and could also be expanded to other types of research and collaboration between OSU and the OSHN hospitals. Development of infection control policies, prevention strategies and performance improvement projects
must fully leverage existing technology while capitalizing on innovative technologies (such as GIS and SNA) in order to properly and adequately address the unique strengths and challenges of both rural and urban medical centers. These types of collaborative efforts and forward thinking programs are required to fully address the morbidity and mortality associated with MRSA.


Australian Society for Microbiology. Molecular structure of MRSA, Retrieved from URL: http://www.asig.org.au/?page_id=197 on 7/1/11

Australian Society for Microbiology. Molecular structure of Staphylococcus aureus, Retrieved from URL: http://www.asig.org.au/?page_id=197 on 7/1/11


Collen, MF. 1995. History of Medical Informatics. AMIA Bookscrafrt INC.. Indianapolis, IN


Dorland WA. Dorland’s Medical Dictionary, 2000. NY; Saunders.


Gorbach SL, Bartlett JG, Blacklow NR. Infectious Diseases 3rd edition. USA. Lippincot Williams & Wilkins: P. 397 – 398.


Korczak D, Schöffmann C. Medical and health economic evaluation of prevention-and control measures related to MRSA infections or -colonisations at hospitals. GMS Health Technology Assessments. 2010 Mar 16;6:Doc04.


McDonald CJ. The barriers to Electronic health records and how to overcome them. JAMIA. 1997;4:213-221.


President’s Council of Advisors of Science and Technology. Report to the President realizing the full potential of health information technology to improve healthcare for Americans: the path forward. Executive Office of the President.2010. Retrieved from URL: http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-health-it-report.pdf on 7/5/11.


Shopin B, Kreiswirth BN. Molecular Epidemiology of Methicillin-Resistant *Staphylococcus aureus*. Emerging Infectious Diseases.2001. 7(2):323-326.


US Congress. ARRA. Retrieved from URL: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_bills&docid=f:h1enr.pdf on 7/10/11.

Vermont Program for Quality in Health Care, INC. VT healthcare associated MDRO Prevention Collaborative Retrieved at URL: http://www.vpqhc.org/interior.php/pid/13/sid/188 on 7/1/11


Weniger A. Health Information Exchange eHealth Initiative Toolkit. NCHICA Annual Conference. 9/11/06. Retrieved form URL: http://www.nchica.org/Past/06/presentations/Weniger2.pdf on 7/10/11


Appendix A: Memorandum of Understanding
Memorandum of Understanding

I. Parties to the MOU

This document is written to describe a Memorandum of Understanding between XXXXXX Hospital (hereafter referred to as “the Hospital”) and the Ohio State Prevention Epicenter (hereafter referred to as “the Epicenter”). Interactions and data sharing between hospitals within the Ohio State Health Network (OHSN) will continue as according to current OHSN rules and are not directly effected by this MOU.

II. Duration of the Agreement

The duration of the MOU is the duration of the CDC funding provided to the Epicenter, at least until January 31, 2011. If funding is extended beyond this date then the agreement may also be extended to match the funding extension.

III. Program Description

The goal of this collaborative agreement is to enhance the infection control and antimicrobial management programs of the Hospital while participating with the Epicenter in conducting epidemiologic research. Research efforts will focus on enhancing our understanding of infection surveillance using electronic and other health data and implementation of strategies for the prevention of infections and spread of antimicrobial resistance. The goals will be accomplished by the enhancement of surveillance for healthcare associated infections (HAIs) and antimicrobial utilization, and by conducting performance and quality improvement projects. In order for full participation, the Hospital will need to become a recognized research site of The Ohio State University (OSU). This will require the acquisition of a Federal Wide Assurance (FWA) number, designation of a person at the Hospital as the Human Protections Administrator, designation of OSU as the IRB affiliated with the FWA, and a site visit from the OSU Institutional Review Board (IRB) for final approval. Both parties will agree to the protocol for each collaborative project and all collaborative projects between the Hospital and the Epicenter will be subsequently approved or exempted by the OSU IRB. Each project will then be conducted exactly in accordance with the OSU IRB approved protocol. Completion of the projects will typically require the sharing of hospital, infection control, antibiotic utilization, and other patient data in the form of a limited data set or fully de-identified and/or aggregated data set as approved by the IRB and in compliance with HIPAA regulations. The Hospital may also be asked to complete surveys related to their demographics or practices which will be aggregated or de-identified as approved by the IRB and in compliance with HIPAA regulations.

IV. Participation by MOU Parties

Performance and quality improvement projects
Improved surveillance of HAIs and antimicrobial utilization
Prevention of HAIs and antimicrobial resistance
Sharing of infection control, antimicrobial use, and patient data

V. Benefits to the MOU Parties

The Hospital will receive logistic and educational support, training, surveillance tools, and infection control and antimicrobial use interventions designed to enhance their infection control and antimicrobial management programs. This support will be provided directly from the
Epicenter by teleconference, electronic transmission, regular mailings, videoconferencing, Webinar sessions, or face-to-face meetings. The Epicenter will benefit from the research data and information provided in keeping with the goals of the CDC-funded Prevention Epicenter program.

VI. Compensation

Education materials, surveillance tools, intervention materials, etc required for successful completion of the project will be provided by the Epicenter to the Hospital. There will otherwise be no financial compensation provided to the Hospital for participation in these projects and no financial support for additional hospital personnel or staff will be provided.

VII. Dispute Resolution

Any difficulties that arise from this MOU will be resolved between the Hospital CEO/Administrator, the Epicenter Principal Investigator and the Executive Director of the Ohio State Health Network.

VIII. Modification/Termination

This MOU constitutes the entire agreement between the parties hereto. This MOU may be modified, altered, revised, extended, or renewed by mutual consent of all parties, by the issuance of a written amendment, signed and dated by all the parties.

CEO/Administrator
XXXXXXX Hospital

Kurt B. Stevenson, MD, MPH
Principal Investigator
Ohio State University Prevention Epicenter

Joann G. Ort
Executive Director
Ohio State Health Network
Appendix B: Standard Operating Procedure (SOP)
STANDARD OPERATING PROCEDURES FOR RESEARCH CONDUCTED BY OSU DIVISION of INFECTIOUS DISEASES AND OHIO STATE HEALTH NETWORK PARTICIPATING CENTERS

Barnesville Hospital
Bucyrus Community Hospital
Madison County Hospital
Mary Rutan Hospital
Mercer County Community Hospital
Twin City Hospital
Wyandot Memorial Hospital
Ohio State University Health System
The Ohio State Health Network (OSHN) is a membership organization that provides cost savings solutions; education and professional networking opportunities to identify and/or develop best practices. The member hospitals include: Barnesville Hospital, Bucyrus Community Hospital, Madison County Hospital, Mary Rutan Hospital, Wyandot Memorial Hospital, Mercer Health, and Twin City Hospital, in addition to Ohio State University Health System (OSUHS). As a part of the CDC Prevention Epicenter Program, The OSUHS is collaborating with the OSHN in conducting infection control analyses and interventions, specifically evaluating the transmission of antimicrobial resistant bacterial pathogens between these facilities and associated communities and OSUHS. Initially we will focus on methicillin-resistant *Staphylococcus aureus* (MRSA) by conducting traditional epidemiologic studies, electronic surveillance, molecular genotyping, geocoding, and social networking of MRSA isolates and cases. The goals of this study include: identifying and investigating MRSA infections at OSUHS and the OSHN by collection of epidemiologic data on cases, molecular identification of MRSA isolates, and determining transmission patterns by utilization of social network analysis and geographic information systems (GIS). The OSUHS intranet connection currently provides access to patient education materials, critical pathways, journals, and textbooks by the OSHN. It is through this intranet connection that selected electronic data elements from each participating outreach facility can be uploaded for infection control surveillance into a designated data mart under the control of the OSUMC Information Warehouse (IW). This is strictly a retrospective review of existing healthcare data and will be presented in an aggregated, de-identified format. This study involves no direct patient contact. It requires medical record review as described in the application and research protocol. The medical record data to be collected will include, but are not limited to patient demographics, medical comorbidities, infection control, laboratory, microbiology, radiology, vital signs, pharmacy, and geocoding data. The study will also analyze MRSA molecular genotype and characterize clonal features and distribution at the hospital or community level using geocoding methods and links between cases by social network analysis. The infection control practitioners at OHSN hospitals will gather much of the patient data and forward data and isolates to OSUHS and Ohio State Epicenter investigators following the OSU Institutional Review Board (IRB)-approved protocol and as outlined in this standard operating procedures (SOPs) here. The Ohio State Epicenter investigators will also collect and handle data as outlined in the OSU IRB-approved research protocol.

A copy of these SOPs for all participating centers will be provided to all engaged research personnel. Receipt of the SOP copy by each research will be documented by their signature on a receipt form and will be maintained in the regulatory files in the Infectious Diseases office.
The SOP will be updated as necessary and a copy of the revised document will be distributed to all above-named personnel.
TRAINING REQUIREMENTS

All employees who will be participating (engaged) in research activities will receive training in the following areas prior to implementation of the protocol.

Human Subjects Protection Training:

All OSU faculty staff and students who conduct or participate in the execution of research projects will receive training in the protection of human subjects. The University uses the web-based Collaborative IRB Training Initiative (CITI) courses to meet this requirement. Applicable OSU personnel take an initial training curriculum and a refresher course every three years thereafter. All OSU faculty, staff, and students engaged in research at the performance site will take the CITI course.

The investigators and research personnel at each participating site in the research project must also complete the CITI course requirements as listed above. The web site for CITI training can be found at: [http://orrp.osu.edu/irb/training/](http://orrp.osu.edu/irb/training/). The course title is “Basic Human Research Course”. Once the course is completed a copy of the course documentation must be forwarded to the OSU project staff to be stored with the regulatory files in the Infectious Diseases office.

Protocol Training:

Protocol-specific training, including completion of required source documents and specific procedures, will be provided by the principal investigator or his/her designee (typically OSU Clinical Research Specialist).
STUDY START-UP

Protocol Approval
All protocols will be reviewed and approved by the OSU Biomedical Sciences Institutional Review Board (IRB) prior to implementation of the research and on an ongoing basis as established by the IRB during its initial review (e.g. every 6 or 12 months).

Regulatory Documents:
All research protocols have required regulatory documents, including but not limited to IRB approvals, template consent forms (if applicable), credentials of research personnel, and required Federal agency forms (i.e. 1572), if applicable. These documents are prepared by the PI with assistance from other team members and submitted in a timely manner. All documents will be securely locked in the Infectious Diseases office. Communication between investigators will be through a secured OSUMC network.

Research Contracts:
Details of data sharing and participation in the designated research can be found in the Memorandum of Understanding previously agreed upon by all participants. All other details of the research are as outlined in the research protocols approved by the OSU Biomedical Sciences IRB.
Source Documentation:

Source documents are defined as original documents where subject information is entered for the first time. Some examples of source documents are a clinic progress note, nurses’ notes, a consent form, a handwritten note with a patient’s weight recorded, laboratory reports, and print outs from testing equipment. The importance of the source document is to be able to recreate the subject’s participation in the research (aside from data sheets or case report forms which are used to compile research data) and to provide documentation or ‘proof’ of the results recorded for research purposes. Such documents are typically filed in the patient medical chart unless they are specific only to research. In that case, they will be stored in the subject’s research chart. Data collected by the OHSN staff as part of the epidemiologic investigation will be kept separate from patient records and hard copies of data collection forms or materials will be kept in a locked file under the control of the site investigators. This information will be either sent to the OSUMC IW in hard copy for data entry or uploaded electronically into the IW for storage and subsequent analysis.

Subject Related Record Keeping and Confidentiality of Subject Data:

Data will be collected by individuals at each site who have institutionally-approved access to patients’ clinical data and who routinely collect these data for infection control and quality improvement activities. Site staff will abstract data from electronic medical records and hospital and clinic charts while maintaining confidentiality standards according to their facility’s policies as well as state and federal regulations. Data will be sent to the OSUMC Information Warehouse (IW) using a secure T-1 line. At the IW they will be assigned a unique identifier code (ID code) by the OSUMC IW Personnel to remove any identifiers. The de-identified data will be made available to the OSU Epicenter investigators for evaluation. The IW will maintain the key to the code and will share the key with the OSU Clinical Research Specialist only to be certain that all cases are accounted for and assigned the correct code and that none are duplicated in the analysis scheme. This is strictly a retrospective review of existing healthcare data and will be presented in an aggregated, de-identified format. This study involves no direct patient contact. It requires medical record collection only as described in the application and research protocol. Therefore, HIPAA waiver has been requested in IRB application.

Study Correspondence:

All communication with sponsor and their affiliates is filed in the Study Binder under the correspondence section.
**Specimen Transport and Storage:**

This study will also analyze MRSA molecular genotype and characterize clonal features and distribution at the hospital or community level using existing MRSA isolates. The Microbiology labs of the site facilities will follow standard packing and shipping of isolates according to state and federal shipping regulations. Isolates are de-identified at the site microbiology labs prior to transport to OSU MC. The specimens will be stored de-identified in a separate freezer in the OSUMC microbiology lab.

**IRB Communication:**

Communication with OSU IRB is ongoing during the course of the study and is the responsibility of the OSU PI/designee and/or OSU Clinical Research manager.
SUBJECT MANAGEMENT

Screening:
Subjects will include patients ≥ 18 years admitted to OSHN during the study period who had a positive MRSA isolate. Because any patient admitted, regardless of age, gender, race, ethnicity, or other characteristics is at risk for the development of a MRSA, all patients admitted OSUMC units and OSHN are included in this study. Given restrictions on the use of data regarding prisoners, any cases determined to be prisoners will be excluded. All efforts will be made to not knowingly collect data on any prisoners in this retrospective review. Subjects will be identified by OSUMC Information Warehouse, OSUMC Clinical Microbiology Department, and OSUMC Clinical Epidemiology Dept and OSHN microbiology laboratory and infection control practitioner.

Informed Consent:
This is strictly a retrospective review of existing healthcare data and will be presented in an aggregated, de-identified format. This study involves no direct patient contact. It requires medical record collection only as described in the application and research protocol. Waiver of informed consent is being requested in the IRB application.

Data Collection and Data Entry:
Research personnel at each site will abstract data from electronic medical records and hospital and clinic charts using a data collection sheet. Hard copies of data collection forms or materials will be kept in a locked file under the control of the site research personnel. Data will be sent to the OSUMC Information Warehouse (IW). At the IW they will be assigned a unique identifier code (ID code) by the OSUMC IW Personnel to remove any identifiers. The de-identified data will be made available to the OSU Epicenter investigators for evaluation. The IW will maintain the key to the code. These de-identified data will be uploaded in a spreadsheet or relational database, pass code protected, on the OSUMC secure computer system. The code containing patient identifiers linked to the “ID Code” will be kept in a secured and locked location in the OSUMC IW. After the data collection is deemed complete then the Key to the ID Code will be destroyed.

Unanticipated Event Reporting:
Adverse Events
All adverse events of non-serious nature will be documented in patient chart, CRF or database with full details and will be followed to resolution if possible. Resolution data will be obtained by the end of study to determine if further follow-up is necessary.
Serious Adverse Events and Unanticipated Events

This is strictly a retrospective review of existing healthcare data and will be presented in an aggregated, de-identified format. This study involves no direct patient contact. It requires medical record collection only as described in the application and research protocol. The medical record data to be collected will include infection control, laboratory, microbiology, radiology, vital signs, and medical records. Medical record data with PHI will be protected as described. Thus, the major potential risk to the patient is the inadvertent or accidental release of confidential patient information during the data collection and measurement. Strict measures are in place in this project to prevent a breach of confidentiality.

The OSU ORRP policy for unanticipated event reporting is located at the following link: http://orrp.osu.edu/irb/forms/EventReporting.pdf.
DATA MANAGEMENT

Record Storage:

The OSUMC IW will maintain identifiable patient data in a secure data mart. These data will include OHSN patients. Under the umbrella of their Honest Broker status they will de-identify the data and assign each case a unique identifier code and provide to the OSU Epicenter investigators. All data will be entered into a pass-code protected spreadsheet or relational data base stored behind the OSUMC firewall. Hard copies of data collection forms or materials will be kept in a locked file under the control of the site research personnel. The OSUMC IW will also generate a unique identifier code for OSUMC patients to allow the OSU investigators to identify patients for access to data collection and medical record review. The key to this code will be kept separate from the data collection. All data entered into the data base and used for analysis will use the unique identifier code and, as such, will be de-identified. Final data analysis will be aggregated and de-identified. After data collection and analysis is completed, the key to the code will be destroyed. These steps will ensure the protection of the participant’s confidentiality.

Research Record Retention:

Upon completion of study, presentation and publication, all documents with patient identifiers will be destroyed. OHSN infection control personnel may keep the identity of the patients whose data have been collected for the sole purpose of infection control and quality improvement. Patient confidentiality will be strictly maintained. This is the responsibility of all research staff. Only study research personnel and investigators will have access to patient data. A unique case number will be given to each patient. No patient identifier will be listed on data abstraction sheet. All documents will be securely locked in the Infectious Diseases office. Communication between investigators will be through a secured OSUMC network.

The PI is responsible for this action at the close of a study. These documents are retrieved at the time of an audit and made available to auditors.
STUDY CLOSE-OUT

Study will be completed after analysis of data collected through 06/30/2010. All study sites (OSHN) and associated research investigators and IRB will be notified upon completion of study. All documents with patient identifiers will be destroyed. Only study investigators will have access to patient data. No patient identifier will be listed on data abstraction sheet. All documents will be securely locked in the Infectious Diseases office.

A summary report of all findings in an aggregated and de-identified form will be shared with the other investigators participating on this CDC-funded collaborative Epicenter program for comparison between centers. This is the format that data will also be submitted for presentation at national meetings and for final publication in peer-reviewed journals. If actual data is requested, the relational database or spreadsheet which contains only de-identified data elements will be provided. Data that is obtained will not be released until it is de-identified.
Appendix C: IRB approval
November 13, 2008

Protocol Number: 2008H0275
Protocol Title: THE OHIO STATE HEALTH NETWORK INFECTION CONTROL COLLABORATIVE-UNDERSTANDING TRANSMISSION OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA), Kurt B. Stevenson, Preeti Pancholi, Nan-Hua Wang, Internal Medicine

Type of Review: Initial Review
IIRB Staff Contact: Carolyn Hagopian
614-292-0169
Hagopian.5@osu.edu

Dear Dr. Stevenson,

The Biomedical IRB APPROVED the above referenced protocol.

Date of IRB Approval: November 10, 2008
Date of IRB Approval Expiration: November 10, 2009

In addition, in addition, the protocol is approved for a waiver of the consent process and a waiver of HIPAA Research Authorization (entire research study).

If applicable, informed consent (and HIPAA research authorization) must be obtained from subjects or their legally authorized representatives and documented prior to research involvement. The IRB-approved consent form and process must be used. Changes in the research (e.g., recruitment procedures, advertisements, enrollment numbers, etc.) or informed consent process must be approved by the IRB before they are implemented (except where necessary to eliminate apparent immediate hazards to subjects).

This approval is valid for one year from the date of IRB review when approval is granted or modifications are required. The approval will no longer be in effect on the date listed above at the IRB expiration date. A Continuing Review application must be approved within this interval to avoid expiration of IRB approval and cessation of all research activities. A final report must be provided to the IRB and all records relating to the research (including signed consent forms) must be retained and available for audit for at least 3 years after the research has ended.

It is the responsibility of all investigators and research staff to promptly report to the IRB any serious, unexpected and related adverse events and potential unanticipated problems involving risks to subjects or others.

This approval is issued under The Ohio State University's OERP Federally Assured #00006378.

All forms and procedures can be found on the OERP website – www.orrp.osu.edu. Please feel free to contact the IRB staff with any questions or concerns.


Karla Zadhil, OD, PhD, Chair
Biomedical Institutional Review Board
Appendix D: Data collection form and dictionary
Section I: To be collected by ICP (site investigators) and sent to OSUMC IW ASAP (via One Source program) upon notification of positive MRSA culture. (Data in this section is made available only to OSUMC IW). This information is used to create a record with a de-identified code which will be used for this patient throughout the study.

- Demographics
  - **Hospital**: name of your facility (on One Source, this is automatically populated in the field for you.
  - **Name**: enter patient’s first and last name
  - **Full address**: Enter patient’s full address. Do not use PO box as the full address is needed for the census tracking software.
  - **Date of Birth**: Enter the patient’s date of birth
  - **Lab specimen #**: Enter the number that you lab assigns to the specimen. This is usually the lab accession number.
  - **Date of specimen**: Enter the date the specimen was collected
  - **Time of specimen**: Enter the time the specimen was collected
  - **Type of specimen**: select the type of source of the specimen. (blood, sputum, urine, stool, skin and soft tissue, and other—if you select “other” please fill in what type)

Section II: To be collected by ICP (site investigators) and sent to OSUMC IW after chart review. (De-identified data in this section is made available to OSU Epicenter Investigators through OSUMC IW.)

**Assigned code from OSU IW** The “assigned code” is the de-identified code that the OSU Information Warehouse generates for each case.

- **Microbiology**
  - Source of MRSA positive culture (check one): (Pick the classification of the source of the infection)
    - **primary bacteremia** (catheter related or unknown source that is not related to an infection from another site)
    - **secondary bacteremia** (blood infection that is related to an infection at another site such as: surgical site infection, lung infection, bone/joint infection, vascular, soft-tissue infection)
    - **Other non-bacteremic** (infection that is not associated with the blood such as: skin/soft tissue, respiratory, urine, other)
Drug susceptibility: enter the results of the sensitivity testing (those listed are the only ones of interest at this time):

- ATB sensitivities (S, I, R)  
  - MIC  
    - oxacillin  
    - erythromycin  
    - clindamycin  
    - tetracycline  
    - rifampin  
    - moxifloxacin  
    - gentamicin  
    - vancomycin  
    - linezolid  
    - quinupristin-dalfopristin  
    - trimethoprim/Sulfamethoxazole  
    - daptomycin  
    - nitrofurantoin

Previous MRSA positive cultures in the preceding 12 months? Complete the sensitivity testing, if known, if the patient had a positive culture in the previous year.

- circle one: Yes No Unknown
- If yes: ATB sensitivities (S, I, R) MIC
  - oxacillin  
  - erythromycin  
  - clindamycin
- Previous MRSA screens in the preceding 12 months. Circle yes if the patient had a positive screening for MRSA in the last year. We do not need sensitivities for this.
  - Circle one: yes no

- **Socio-demographic**
  - Sex: male female (Circle one)
  - Race and ethnicity (check all that apply)
    - Race
      - American Indian or Alaska native
      - Asian
      - Black or African American
      - Native Hawaiian or Other Pacific Islander
      - White
  - Ethnicity (do not guess, leave blank if not written in chart)
    - Hispanic or Latino
    - Not Hispanic or Latino

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Family and social history— if known, check if patient has ever had a history of any of the following:

- Hx: (check all that apply)
  - Injection drug use
  - Tobacco
  - ETOH use
  - Incarceration
  - Other ________________________

- Occupation:  enter if known

Healthcare-associated Risk factors present in the 12 months preceding the culture. (check all that apply). Check if patient has had any of the following in the last year:

- presence of an invasive device (e.g., vascular catheter, G-tube)
  - specify type of device: ________________________

- history of MRSA infection or colonization

- surgery

- hospitalization

- dialysis

- residence in a long-term care facility (like skilled nursing or nursing home)

- Other ________________________

Clinical information:

- Admission and Discharge Diagnosis (enter the primary dx and 5 secondary dx that was assigned after discharge)

  - Primary dx: __________________________________________

  - Secondary dx:
    - __________________________________________
    - __________________________________________
    - __________________________________________
    - __________________________________________

- Past medical history (check all that apply—if have ever had any of the following conditions in their lifetime)

  - endocarditis
  - renal failure
  - cirrhosis
  - neoplasms
  - immunosuppression
  - diabetes mellitus
  - chronic lung disease
  - transplantation
☐ AIDS
☐ other: __________________________

- Past surgery history (check all that apply—if have ever had any of the following conditions in their lifetime)
  - past trauma
  - orthopedic prosthesis
  - cardiac prosthesis
  - Other: __________________________

- Clinical symptoms (check all that apply)
  - Fever
  - Other: (list any other symptoms of importance such as redness, swelling, purulent drainage, etc)

- Invasive devices within 7 days prior to infection (check all that apply)
  - hemodialysis
  - tracheostomy
  - endotracheal tube
  - mechanical ventilator
  - central venous catheter
  - total parenteral nutrition therapy
  - Swan-Ganz catheter
  - Foley catheter
  - drainage tubes
  - Other: __________________________

- Laboratory Tests
  - CBC with diff (enter values if known use the results that are closest in date to the +MRSA culture, should be within a week of the culture)
    - WBC ____
    - RBC ____
    - HGB ____
    - HCT ____
    - MCV ____
    - MCHC ____
    - RBC distribution _____
- Platelets _____
- MPV _____

- Differential:
  - Neutrophils _____ %
  - Lymphs _____ %
  - Mono _____ %
  - Eosinophils _____ %
  - Baso _____ %
  - Neutrophils absolute ______
  - Lymphs absolute ______
  - Monos absolute ______
  - Eosinophils absolute ______
  - Baso absolute ______

- comprehensive metabolic panel
  - Sodium ______
  - Potassium ______
  - Chloride ______
  - Carbon Dioxide ______
  - BUN ______
  - Creatinine ______
  - BUN/Creatinine ______
  - Glucose ______
  - Magnesium ______
  - Calcium ______
  - Anion Gap ______
  - Osmolality (Calc) ______
  - Bilirubin, Total ______
  - Bilirubin, Direct ______
  - Protein, Total ______
  - Albumin ______
  - GGT ______
  - ALT ______
  - AST ______
  - LD ______
  - Amylase ______
  - Lipase ______

- HIV (reactive/nonreactive)
- CD4 count
  - <50
  - Other: ______________

- Viral load: ______________
- Other Microbiology results: (enter any other positive cultures from this admission)

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<th>Date:</th>
<th>Source:</th>
<th>Organism:</th>
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- Radiology results (CXR or CT chest or “other radiology”) List name of test and results from this admission if they are pertinent to the MRSA infection (i.e. CXR if MRSA pneumonia).
  - Circle one: Normal abnormal
  - If abnormal write impression:
    ___________________________________________________________
    ___________________________________________________________
    ___________________________________________________________
    ___________________________________________________________

- Antibiotic Regimen and duration (for this admission, if more than 4 just use drugs against MRSA)

<table>
<thead>
<tr>
<th>Name of drug:</th>
<th>Dosage:</th>
<th>Start Date:</th>
<th>Stop Date:</th>
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<td>Strength:</td>
<td>Frequency:</td>
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- Complications of treatment (list any complications from this admission if known)
  - Circle one: Yes No Unknown
  - If yes, type of complication (check all that apply)
    - Renal failure
    - Liver failure
    - Neutropenia
    - Thrombocytopenia
    - Thrombotic event
    - Other: ________________________________
- Outcome (check one): *(list the outcome if known)*
  - Cure (complete resolution after antibiotic treatment)
  - Failure (persistence of infection and requirement of change in antibiotics)
  - Relapse (resolution of infection after complete treatment then new symptoms appear)
  - Recurrent (redevelopment of MRSA at same or other site > 2 weeks post treatment)
  - Indeterminate (unknown outcome)
  - Death (30 days mortality due to any causes)

- Epidemiology data
  - Date and Time of notification of MRSA culture isolation to medical staff
    (enter the date and time of when the physician or nursing staff was notified of results, if known)
    - Date: ____________
    - Time: ____________
  
  - Date and Time of isolation precautions ordered/implemented
    (enter the date and time of when the patient was placed in precautions, if known)
    - Date: ____________
    - Time: ____________

  - Date and Time of Admission
    (enter admission date and time)
    - Date: ____________
    - Time: ____________

  - Length of hospital stay
    (enter the length of stay if patient received inpatient care)
    - #days if known______

  - Inpatient admit service (check one)
    (enter type of unit patient was admitted to)
    - Medical
    - Surgical
    - OB/GYN
    - Intensive Care
    - Other specialty care unit: ________________

  - Inpatient location(s) (check all that apply)
    (check any other type of unit that patient stayed)
    - Intensive care unit
    - Patient care unit
    - Long-term care unit
- Other:_________________

- **Outpatient location:**
  - Emergency Department
  - Outpatient Clinic
  - Home
  - Other: (specify)________________

- **Pre-admission location(s) in last 4 weeks (will need name and address of each)** Enter where the patient stayed in the last 4 weeks if known.

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<tr>
<th>Date(s)</th>
<th>Location:</th>
<th>Name:</th>
<th>Address:</th>
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<tbody>
<tr>
<td>Home</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Skilled nursing facility or rehab facility</td>
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<td>Referral hospital</td>
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<td>Other:</td>
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- Patient disposition to (check one): (check where patient was discharged to, if known)
  - not discharged
  - home
  - skilled nursing or rehab center
  - other hospital
  - n/a (use this if patient expired)

- Hospitalizations in the preceding 12 months? (List dates of any admissions in the past year)
  - Circle one: Yes no Unknown
  - If yes, list dates and location if available:
    - ________________________________________________
    - ________________________________________________
    - ________________________________________________
    - ________________________________________________

- Classification (check one): (choose which classification fits patient best)
  - **Healthcare- associated (HA)** – culture obtained greater than 48 hours after admission, with or without healthcare-associated risk factors.
  - **Healthcare-associated Community Onset (HACO)** – culture obtained ≤ 48 hours after admission with identified healthcare-associated risk factors (for example, has had recent healthcare inpatient visit or surgery).
  - **Community- associated (CA)** – culture obtained ≤ 48 hours after admission without healthcare-associated risk factors (for example, has NOT had any recent healthcare visit or surgery)
• Geocoding: (To be completed by OSUMC IW and OSU Epicenter Investigators)
  ▪ Zip Code: _____________________
  ▪ Census Tract: _________________________________________________________

• Genotype: (To be completed by OSUMC IW and OSU Epicenter Investigators)
  □ Rep PCR type _______________
  □ PFGE type _________________
  □ Other: (specify): ____________ type: ___________

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<tr>
<th>Test Name</th>
<th>Result</th>
<th>Lab Name</th>
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Appendix E: Instructions to run query to get OSUMC positive MRSA cases
Instructions to run query to get OSU positive MRSA cases:

1. Open One Source and type IW into browser address window.
2. Then click on "Discoverer Viewer."
Sign in using your MedCenter login

Sign in again using your MedCenter login

Type “Encounter” in Database field and hit enter
Click on arrow to expand list to see the available queries

Click on the link to run the query

Enter the start and end date needed using format of two digit day-first three letters of month-four digit year: DD-MON-YYYY

And click on “Go”
After a couple of minutes the list will appear at the bottom of the page. You can then export the list into Excel by clicking on the Export link.

Select “CSV (Comma delimited)” and then Export.

Once completed, click on “Click to view or save.”
*Click on SAVE (save as either: OSU MRSA or OSHN with today’s date (example: OSU MRSA.03-09-09 or OSHN MRSA.03-09-09 if saving the targeted zip codes).

Then you can open the file.

Once you have list in Excel, double check that all specimens are positive for MRSA.

Delete all MRSA screenings since we are just testing actual infections.

Then copy and paste rows into the master spreadsheet and highlight all duplicate cases.
Select the cases to be tested according to the outlined procedure and transfer appropriate information to master lab spreadsheet and e-mail to Ruchi Soni (ruchi.sonii@osumc.edu) in the lab by 2:00 pm on Mondays and Thursdays. 

(See separate detailed instructions)

**troubleshooting:** If query times out before it has completely run, expand the number of minutes to time out under “preferences”
Appendix F: Instructions for getting de-identified code
Instructions to get de-identified code for a positive MRSA culture

1. Open "One Source" and type https://www.osumc.edu/Applications/MRSA

   OR

   Click on Clinical Applications under "Quick Access" menu and find "EPICENTER MRSA Project"

2. Enter the MedCenter logon ID and password that OSU provided to you
3. Under the “Search” tab--

Search for the patient to determine if they already have a code assigned to them. This can be accomplished in 4 different ways:

• Search by MRN
• Search by Last name
• Search by Assigned code (if you already know this)
• Click on “View All” button and look through the list to find the patient’s name.

If you select “View all”, all the records that have been entered will appear as a line listing below the search box.
If the patient does not have a code yet and you need to enter a new record, click on the "Add Spec." tab.

To open a case that you have already entered, click on the "code" number link.

These two columns will show if you have completed the survey or not. (More on that function later—it is not completely developed yet.)
If you select “Add Spec.” tab, this screen will appear and you will enter all the required information:

After you enter all the required data and click on “save” the code number magically appears here.

Your hospital name should default here.

Enter the patients Medical Record Number here.

Enter Patients name and full address here.

Enter the patient’s birthdate (MM/DD/YYYY) or select from calendar (see directions on next page).

Enter the lab ID number of the specimen that your hospital assigned.

Enter the date the specimen was collected (MM/DD/YYYY) or select from calendar.

Enter the time the specimen was collected HH:MM and click on AM or PM.

Click on the type of specimen.

If you select “Other” please type the description in this box.

When all fields are completed click on the “Save” button. Your de-identified code will appear at the top of the screen in blue. This is the number to write on the label of the specimen to send to OSU.

**NOTE** if you did not complete all of the fields correctly, the code will not appear and a note in red letters will appear next to the field that is entered incorrectly. Once you correctly enter all the fields, click on save again and the code will appear.
Using the Calendar (ICON) function (optional):

You can either fill in the date (MM/DD/YYYY) or click on the calendar icon. Then, the current month calendar appears; just click on the day, and it will automatically fill in the date.

To show the entire year, click on the title again.

To show the decade, click on year again.

Use the side arrows to go forward or backwards until you find the right year. Then, click on the month and day that you are searching for.
Appendix G: Process for obtaining OSU PCR list for targeted zip codes
Process for obtaining list for PCR testing of OSU inpatients: 
Targeted Zip Codes “the Outreach areas”

1. Obtain the full list of positive MRSA specimens for the targeted zip codes for the specified time frame. (prisoners and patients < 18 yrs old have been removed by IW through the query)
   a. Run query (see separate instructions: “Instructions to run query to get OSU positive MRSA cases”)
   b. Export to Excel

2. Double check that all specimens are positive for MRSA
   a. Delete all sources labeled: *MRSA*Anterior*Nares*(PCR) or “Screen”

3. Sort list by last name and highlight list in purple

4. Then look at the list to see if any of the patients had more then one culture on the list. If so, highlight all but one record in orange to show that it’s repeated or delete any cultures that are an exact duplicate (have same lab ascension number).
   a. If the patient has any blood cultures we prefer to use that one for testing.
      If no blood cultures were tested just keep the first culture obtained for that patient.
   b. **Please try not to use cultures that say “For Susceptibilities SEE” or “For Susceptibilities REFER TO” after Staphylococcus aureus: METHICILLIN RESISTANT in the Test_Rslt column. This means the susceptibilities were not performed on this specimen and refers to another plate (which is usually thrown away by the time we need to retrieve it).**

5. Copy cases to master file under tab called: targeted zip codes
   (K:\EPIDEM\DATABASE\CDC Epi-Center Grant\Outreach Project\MRSA_GIS project\OSU prospective MRSA isolates\PCR master testing list)
   a. Expand the chronological numeric numbering in column A to encompass the added records.
   b. Then sort entire list by last name and compare the names in purple with the existing records. If you find a record in purple that is the same person as one in Yellow (we have already tested that person) highlight any subsequent cases for that same patient in Orange (indicating it is a duplicate). Please compare the name, address, and MRN to ensure it is the same patient.
   c. Then sort the cases back in numerical order using column A.
   d. Check all addresses to make sure there are no PO Boxes. If you find a PO Box address only without any physician street address unhighlight the purple on that case and keep it on the list.
e. Using the remaining purple highlighted cases, select the cases to have PCR testing completed as outlined below.

6. Select cases to run PCR:
   a. Use **ALL non-duplicated cases** from “Positive MRSA Target Zip Codes”
   b. Highlight all cases selected for PCR testing in yellow. Type “STOPPED HERE” on the last row for that day and then save list.

7. Obtain de-identified code on all selected cases (see separate instructions)
   a. Mark de-identified code on master list and date sending request to lab in the appropriate columns

8. Add cases with de-identified code to master lab spreadsheet
   (K:\EPIDEM\DATABASE\CDC Epi-Center Grant\Outreach Project\MRSA_GIS project\OSU prospective MRSA isolates\PCR testing list for lab)
   a. Info to add to spreadsheet includes:
      i. Last Name
      ii. First Name
      iii. MRN
      iv. Date of Test
      v. Sq_Acsn_No
      vi. Batt_Cd_Desc
      vii. Date MIC finalized
      viii. De-Identified code
   b. Make sure current cases to test are highlighted in yellow prior to sending list to lab
   c. E-mail to OSU lab tech by 2:00 pm on Monday and Thursday of each week.
      d. Then immediately call lab tech to notify her that the list has been sent.

9. Log number of specimens tested on master spreadsheet under the “specimen log” tab.

10. Lab tech will call if she cannot find all the plates. Log those numbers under the “specimen log” tab of the spreadsheet under “rejected”. Write “unable to find plate” under Genotype column in PCR testing list for lab sheet.
Appendix H: Process for obtaining OSU PCR list for targeted zip codes
Process for obtaining list for PCR testing of OSU inpatients:
Non-targeted zip codes

11. Obtain the full list of positive MRSA specimens for the non-targeted zip codes for the specified time frame. (prisoners and patients < 18 yrs old have been removed by IW through the query)
   a. Run query (see separate instructions: “Instructions to run query to get OSU positive MRSA cases”)
   b. Export to Excel

12. Double check that all specimens are positive for MRSA
   a. Delete all sources labeled: *MRSA*Anterior*Nares*(PCR) or “Screen”

13. Sort list by last name and highlight list in purple

14. Then look at the list to see if any of the patients had more then one culture specimen on the list. If so, highlight all but one record in orange to show that it’s repeated or delete any cultures that are an exact duplicate (have same lab ascension number).
   a. If the patient has any blood cultures we prefer to use that one for testing. If no blood cultures were tested just keep the first culture obtained for that patient.
   b. **Please try not to use cultures that say “For Susceptibilities SEE” or “For Susceptibilities REFER TO” after Staphylococcus aureus: METHICILLIN RESISTANT in the Test_Rslt column. This means the susceptibilities were not performed on this specimen and refers to another plate (which is usually thrown away by the time we need to retrieve it).**

15. Copy cases to master file under tab called: non-targeted zip codes
   (K:\EPIDEM\DATABASE\CDC Epi-Center Grant\Outreach Project\MRSA_GIS project\OSU prospective MRSA isolates\PCR master testing list)
   a. Expand the chronological numeric numbering in column A to encompass the added records.
   b. Then sort entire list by last name and compare the names in purple with the existing records. If you find a record in purple that is the same person as one in Yellow (we have already tested that person) highlight any subsequent cases in Orange (indicating it is a duplicate). Please compare the name, address, and MRN to ensure it is the same patient.
   c. Then sort the cases back in numerical order using column A.
   d. Check all addresses to make sure there are no PO Boxes. If you find a PO Box address only without any physician street address unhighlight the purple on that case and keep it on the list.
   e. Using the remaining purple highlighted cases, select the cases to have PCR testing completed as outlined below.
16. Select cases to run PCR:
   a. Use **ALL non-duplicated cases** from “Positive MRSA Target Zip Codes”
   b. Use **all BLOOD cultures** from “Positive MRSA labs” list
   c. Of the remaining “positive MRSA labs” list use **randomly selected** cases to equal a total of 12 – 13 cases a week (or 6 – 7 cases each Monday and Thursday) **if \< 6, test all specimens.**
      i. Run random number generator by entering formula into excel spreadsheet: =RANDBETWEEN(X,XX)
         Where the first X is 1 and the second XX is the total number of specimens for that day. [Example: if there are 25 specimens for that day the formula will be written: =RANDBETWEEN(1,25)] To select 6 cases, you will run the formula 6 times to get the 6 numbers for selection of PCR testing.
   d. Highlight all cases selected for PCR testing in yellow. Type “STOPPED HERE” on the last row for that day and then save list.
   e. Remove the purple highlights off all cases that were not selected for testing for that day and just keep those case’s cells clear (no highlight)

17. Obtain de-identified code on all selected cases (see separate instructions)
   a. Mark de-identified code on master list and date sending request to lab in the appropriate columns

18. Now add cases with de-identified code to master **lab** spreadsheet
   (K:\EPIDEM\DATABASE\CDC Epi-Center Grant\Outreach Project\MRSA_GIS project\OSU prospective MRSA isolates\PCR testing list for lab)
   a. Info to add to spreadsheet includes:
      i. Last Name
      ii. First Name
      iii. MRN
      iv. Date of Test
      v. Sq_Acsn_No
      vi. Batt_Cd_Desc
      vii. Date MIC finalized
      viii. De-Identified code
   b. Make sure current cases to test are highlighted in yellow prior to sending list to lab
   c. E-mail to lab tech by 2:00 pm on Monday and Thursday of each week.
   d. Then immediately call lab tech to notify her that the list has been sent.

19. Log number of specimens tested on master spreadsheet under the “specimen log” tab.

20. Lab tech will call if she cannot find all the plates. Log those numbers under the “specimen log” tab of the spreadsheet under “rejected”. Write “unable to find plate” under Genotype column in PCR testing list for lab sheet.