Resistant *Staphylococcus aureus* Infections in the United States: A New Classification, a New Resistance and the Implications for Surveillance, Prevention, and Control

by

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are often defined as healthcare-associated (HA) or community-associated (CA) based on three different classification schemes: healthcare risk factor, infection type, or susceptibility pattern. This dissertation analyzed the sensitivity, specificity, and utility of these classifications using MRSA case data from Michigan.

MRSA infections were voluntarily reported to the Michigan Department of Community Health (MDCH) from October 2004 through December 2005. Data on patient demographics, risk factors, and infection information were recorded on the MDCH MRSA Report Form and submitted with laboratory susceptibility test results. A total of 2,151 non-duplicate MRSA infections were reported. Pulsed-field gel electrophoresis (PFGE) tests were conducted on 244 randomly selected isolates from reported cases.

The first project classified MRSA infections as HA or CA using each of the three classification schemes, then examined results for inconsistency across methods. Comparison of HA and CA results using the common classification schemes revealed a large proportion of inconsistent results. The second project used PFGE test result as a gold standard to consider the three classification schemes and other important contributing variables aimed at producing an improved multivariable classification model. This new model using infection type, susceptibility pattern, age and hospitalized as variables better predicted PFGE classification of HA or CA than any other single

classification method. The third project evaluated accuracy of the new classification model and used it to define the epidemiology of Michigan MRSA infections. This analysis revealed that MRSA is prevalent across Michigan and CA-MRSA, particularly among males, blacks, people within correctional facilities, and people presenting to emergency departments. A final project produced a comprehensive review of the first seven cases of emergent vancomycin-resistant *Staphylococcus aureus* (VRSA) in the US. All VRSA cases had a history of prior MRSA and enterococcal infection or colonization; all had several underlying conditions and most had received vancomycin prior to their VRSA infection.

In conclusion, the improved method to categorize MRSA infections as HA or CA, and characterization of the VRSA cases, provides new knowledge that will help to accurately target control efforts and prevention methods and messages to better combat this adept and evolving bacterium.

Chapter I

Introduction

The *Staphylococcus aureus* Organism

Staphylococcus aureus is a gram-positive, coagulase-positive, facultatively anaerobic, spherical, bacterium that grows singly, in pairs, and irregular clusters. It is a human commensal organism found on the skin and in skin glands, on mucous membranes, and in the blood, intestinal, genito-urinary, and upper respiratory tracts. It has the ability to colonize an individual for both short and extended periods of time. A recent study has reported that approximately 29% (78.9 million persons) of the United States general population is nasally colonized with *S. aureus* and about 1.5% (4.1 million persons) with methicillin-resistant *S. aureus* [1]. It is an opportunistic pathogen and has long been known as a common cause of human infections. These infections range from minor dermatological conditions to serious systemic illnesses, including small pustules (i.e. pimples), furuncles (i.e. boils), folliculitis, impetigo, scalded skin syndrome, cellulitis, abscesses, osteomyelitis, endocarditis, pneumonia, meningitis, bacteremia, and septicemia.

History of *S. aureus* Resistance

Staphylococcus aureus is a hardy bacterium and also has the ability to develop resistance to the drugs commonly used to treat the infections it causes. Penicillin was first introduced in 1940 and its use dramatically reduced the overall number of bacterial

infections in the U.S. and worldwide. However, it was only four years later, in 1944, when the first penicillinase-producing strains of *S. aureus* were reported [2]. By the late 1940s and early 1950s, most hospital isolates of *S. aureus* were resistant to penicillin [3]. In response to this increasing resistance, scientists created a new class of semi-synthetic penicillin drugs, which included methicillin. Methicillin was introduced in 1960, and in 1961 the first cases of methicillin-resistant *Staphylococcus aureus* (MRSA) were reported from the United Kingdom [4]. Hospitals in the United States were reporting MRSA by the mid-1970s. By the 1990s, MRSA was considered endemic in large urban medical centers in the U.S. [5-9]. Vancomycin became the drug of choice to treat the growing number of nosocomial MRSA infections, and it continues to be a reliable and effective drug for this treatment [10, 11].

As the incidence of MRSA in hospital settings was quickly increasing from the mid-1970s through the 1990s, the first reports of MRSA identified in community settings were published in the early 1980s [12, 13]. MRSA identified within a healthcare setting or among individuals who received recent care from such a setting is referred to as healthcare-associated MRSA (HA-MRSA). MRSA identified among individuals outside of a healthcare setting and who have not received recent care from such a setting is referred to as community-associated MRSA (CA-MRSA). The initial reports of CA-MRSA occurred among injecting drug users. Reports of CA-MRSA infections remained infrequent until 1997, when the deaths of four children in Minnesota and North Dakota brought CA-MRSA to national attention [14]. Shortly after this report, the incidence of CA-MRSA began increasing throughout the United States. The increase in CA-MRSA reporting was a result of both a true spread of this type of MRSA and a new awareness of

its presence. This new CA-MRSA differed from the more common HA-MRSA in that it often occurred among younger individuals who did not have any significant medical conditions or occurrences that required recent interactions with a healthcare facility. As CA-MRSA became more prevalent, outbreaks were reported among children attending daycare, prison inmates, men who have sex with men, and players of competitive sports [15-18].

In 1997, as CA-MRSA reports began increasing, the first clinical case of a HA-MRSA acquiring intermediate resistance to vancomycin was reported in the United States. This vancomycin-intermediate *Staphylococcus aureus* (VISA) infection was reported in a peritoneal dialysis patient from Michigan [19]. Following this initial case, eighteen additional U. S. cases of VISA infection were reported to and confirmed by the Centers for Disease Control and Prevention (CDC) through 2006 [20-23]. The prospect of vancomycin rendered ineffective for treatment of MRSA infections was of serious concern, as it was often the last drug available to treat the highly resistant organisms.

In June 2002 this fear was realized when a Michigan hospital laboratory and the state health department identified and confirmed a hemodialysis patient as the first clinical case of vancomycin-resistant *Staphylococcus aureus* (VRSA) infection in the world [24-26]. Through the end of 2006, six additional, epidemiologically unrelated cases were reported, one each from Pennsylvania and New York, and four from Michigan (Table 1). In addition to the first case, reports had only been published on the second and third cases, with very limited information from the third case [27-30]. Following the full report on the first seven VRSA cases [31], two additional cases were identified from Michigan, in November and December 2007.

First Seven U.S. VRSA Cases, 2002-2006

Case Number	Date	State	Risk Factors
1	June 2002	MI	Hemodialysis Chronic Foot Ulcers
2	Sept. 2002	PA	Morbid obesity Chronic foot ulcers
3	March 2004	NY	Multiple sclerosis Long-term care resident
4	Feb. 2005	MI	Diabetes Gangrenous toe wound
5	Oct. 2005	MI	Morbid obesity Post-op wound infection
6	Dec. 2005	MI	Motor vehicle accident Chronic foot ulcers
7	Oct. 2006	MI	Hemodialysis Chronic ulcers

Mechanisms of Resistance and Genetic Makeup of MRSA

MRSA acquires its resistance via the methicillin resistance gene *mecA*, which encodes a low-affinity penicillin-binding protein PBP2′ (or PBP2a) that is absent in susceptible *S. aureus* strains [32]. This foreign penicillin-binding protein does not bind well to most β-lactams, and therefore allows MRSA to grow in their presence. The *mecA* gene is carried on a mobile genetic element called the staphylococcal chromosomal cassette *mec* (SCC*mec*). Five types of SCCmec (I, II, III, IV a and b, V) have been characterized, each of which differs in size and genetic composition [33]. SCC*mec* II is one of the larger types and has been associated with HA-MRSA infections, along with types I and III. SCC*mec* IV is the smallest type and has been associated with CA-MRSA infections. Its shorter length allows for a much quicker doubling time compared to the HA-MRSA types [34]. This faster doubling time is thought to be a reason for CA-MRSA having a higher prevalence in the community setting and increased fitness in competition

with other bacteria. In addition to the *mecA* gene, some MRSA have the ability to acquire resistance genes from plasmids of other resistant organisms. These acquisitions confer multi-resistance to the MRSA organism and often leave only vancomycin and the newest available drugs (e.g. linezolid, daptomycin, quinupristin-dalfopristin, tigecycline) as effective treatments. The larger HA-MRSA types are associated with multi-resistance, while the shorter CA-MRSA type is usually only resistant to the β-lactams (including cephalosporins and carbapenems) [35-37]. In addition to resistance genes, MRSA organisms are also known to acquire toxin-producing genes. CA-MRSA is associated with these gene acquisitions, and currently the most common toxin produced by this organism is Panton-Valentine leukocidin (PVL) [38]. PVL destroys human leukocytes and alone can cause lesions in the skin. Though MRSA organisms can be very different, there is a certain degree of clonality at the molecular level. In studying chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis (PFGE), the CDC has identified a number of clonal USA strains (100-800) that encompass the majority of MRSA strains identified in this country [39]. USA strains 100 and 200 are the most common associated with HA-MRSA infections and USA strains 300 and 400 are the most common associated with CA-MRSA infections [38, 40-42].

Mechanisms of Resistance for VISA and VRSA

The resistance mechanisms for VISA and VRSA organisms are very different, and subsequently a VISA does not become a VRSA along a simple continuum of increasing resistance. The intense selective pressure from the excessive use of vancomycin in the treatment of an MRSA infection may cause spontaneous genetic mutations in the MRSA organism that are involved with cell wall biosynthesis. When

these genes are expressed there is a thickening of the cell wall, and a decreased peptidoglycan cross-linking as D-alanine binds together in strands. These changes result in a thickened extracellular material that has the ability to sequester vancomycin and hold it outside of the bacterial cell wall, thereby reducing the susceptibility of the MRSA to vancomycin, and creating a VISA organism [43].

For an MRSA to develop vancomycin resistance, there must be colonization or recurrent infections with both MRSA and vancomycin-resistant *Enterococcus* (VRE), often *E. faecalis*. In this mechanism, the *vanA* gene, which mediates resistance in VRE, is transferred via a whole plasmid or just the *Tn1546* transposon from the VRE to the MRSA organism. It is believed that the pressure from excessive presence of vancomycin may play a role in inducing this reaction. Once the *vanA* gene is turned on, it produces a ligase that cleaves a cell wall precursor. This resulting change in the bacterial cell wall renders it incapable of binding to vancomycin, thereby making the new VRSA completely resistant to vancomycin and its effects [26].

Epidemiologic and Molecular Differences Between HA-MRSA and CA-MRSA

As noted in the discussion on "Mechanisms of Resistance and Genetic Makeup of MRSA", there are many distinguishing differences at the molecular level between HA-MRSA and CA-MRSA. In HA-MRSA, the *mecA* gene is often located on SCC*mec* II and the common strains are identified as USA100 and USA200. This organism has a greater tendency to acquire additional resistance genes, which makes it resistant to more classes of antibiotics, including macrolides, aminoglycosides, lincosamides, tetracyclines, folate pathway inhibitors, and fluoroquinolones, but it does not acquire toxin-producing genes, like PVL. In CA-MRSA, the *mecA* gene is usually located on SCC*mec* IV and the

common strains are identified as USA300 and USA400. This organism does not have a tendency to acquire additional resistance genes, so it is often only resistant to β–lactams. However, it does often carry toxin-producing genes, like PVL.

There are also epidemiologic differences between these two types of MRSA, in addition to the molecular differences. The risk factors for HA-MRSA and the groups at risk are those individuals who have within the past year: been hospitalized, undergone surgery, spent time in an intensive care unit (ICU), had an indwelling catheter or medical device, are dialysis patients, or reside in a long-term care (LTC) or rehabilitation facility. These more resistant infections also tend to be more serious clinically, including surgical site, wound, urinary tract, pneumonia, and bloodstream infections. CA-MRSA has an exclusionary definition, that is, the infections aren't associated with the HA-MRSA risk groups. These infections often occur among otherwise healthy individuals and in an outpatient setting or within 48 hours after admission to a healthcare facility. The groups at most risk for CA-MRSA include children attending daycare or school, athletes of close contact sports, correctional facility inmates, military recruits, homeless individuals, injecting drug users, and men who have sex with men. The risk factors for CA-MRSA include close skin-to-skin contact, breaks in skin (cuts, abrasions, skin disease, surgical sites), crowded living conditions, poor hygiene, and contaminated items and surfaces. These less resistant infections tend to be less serious and are often skin and soft tissue infections that may only require incision and drainage without antibiotics. These minor CA-MRSA skin infections are sometimes misidentified as spider bites. The caveat of CA-MRSA is that if left untreated or treated inappropriately, the toxins produced by this

organism can cause major infections with serious damage, including necrotizing pneumonia, severe sepsis, and necrotizing fasciitis [44].

Impact of MRSA

Infection from a resistant organism increases morbidity and mortality risk for the patient as well as healthcare costs. Compared to a methicillin-susceptible *S. aureus* (MSSA) infection, MRSA infections are associated with an increase in severity of disease (APACHE II Classification System), sometimes requiring additional specialized medical treatments (ventilation, surgical debridement, hyperbaric therapy, isolation, etc.), a decrease in options for antibiotic therapy that is more costly, often more toxic to the patient and sometimes not as effective, an increase in hospital length of stay, and sometimes outcomes with debilitating morbidity and even death [45-48]. MRSA continues to remain a growing problem, within our healthcare facilities and in our communities. Surveillance data from the CDC National Nosocomial Infections Surveillance (NNIS) system report showed that from 1998 through 2002, 45%-52% of *S. aureus* isolates collected from infections in ICU patients were MRSA. In 2003, 60% of those isolates were MRSA, representing an 11% increase in resistance in 2003 compared to the mean resistance over the previous five years. NNIS data from 1998 through 2004 revealed that of the number of *S. aureus* isolates tested, the pooled mean percent that were MRSA for ICUs was 53%, for Non-ICU inpatient areas was 46%, and for outpatient areas was 31% [6]. A recent study of MRSA hospitalizations reported an estimated 477,927 hospitalizations with a diagnosis of *S. aureus* infection annually in U.S. hospitals. Of these, approximately 278,203 hospitalizations are related to MRSA. [49]. Additional reports from the CDC stress MRSA as an important cause of morbidity with

an invasive MRSA incidence rate of 19-40/100,000, and a MRSA percentage of *S. aureus* isolates as high as 64% in some hospitals [50].

Michigan antibiogram data indicated an increase in MRSA in Michigan hospitals in 2004 compared to 2003, when the statewide mean was 40% and the range across regions was 25%-52% [51]. The data collected from hospital laboratories in 2004 revealed a statewide MRSA percentage of 50%, ranging from 27%-59%. The southwest region of Michigan had higher prevalences (55%-59%) than the northern Lower Peninsula and Upper Peninsula of Michigan (27%-33%).

MRSA in the community setting has been a growing problem with increasing incidence and prevalence in U.S. communities over the past eight years, and studies specifically looking at this organism have increased. Three states (GA, MD, MN) that participate in the CDC Active Bacterial Core Surveillance (ABCs) project compared data that were collected from 2001-2002 to investigate geographic variability in CA-MRSA, demonstrating a range of 8-20% of reported MRSA, and a CA-MRSA incidence range of 18-26/100,000 [50]. Additional data from the CDC ABCs project, revealed that of the invasive MRSA cases reported in 2005 and 2006, about 14% of the cases were community-associated (CA-MRSA), 26% were healthcare-associated (HA-MRSA) with onset in the hospital, but 60% were healthcare-associated (HA-MRSA) with onset in the community [52]. The area most likely to identify invasive CA-MRSA cases was the emergency department (ED). A study collecting data on skin and soft tissue infections in adult ED patients from eleven sites throughout the U.S., reported a mean of 59% attributable to MRSA, with a range from 15%-74%. Analysis of these MRSA isolates, revealed that 72% of them identically matched the USA300 strain and 25% of them

matched a close variation of this strain, which is the most common CA-MRSA strain in the U.S. [53]. The total number of skin and soft tissue infection-related visits to ambulatory physicians increased from 8.6 million in 1997 to 14.2 million in 2005 (a 65% increase) [54].

Impact of VISA and VRSA

The infection from a VISA or VRSA organism further increases the morbidity and mortality risk and healthcare costs, compared to a MRSA infection. In addition to increased disease severity, there are requirements for specialized medical treatments, requirements for isolation precautions and dedicated staff and equipment, length of hospital stay increases, and the decrease in options for antibiotic therapy becomes even more costly and critical to the patient as well as the community as a whole. Vancomycin is lost as an effective treatment for the infection, when a MRSA organism makes the transition to a VISA or VRSA organism. This impact is critical for two major reasons. First, vancomycin is a highly utilized antimicrobial agent and is effective for the treatment of a variety of infections. It is the most effective and reliable drug for treatment of HA-MRSA and it remains the drug of choice for these infections. NNIS data from the 2004 report show that vancomycin is ranked most often as the third or fourth most utilized antimicrobial agent in nine critical healthcare units and wards, including coronary care, cardiothoracic intensive care, hematology/oncology/transplant, medical intensive care, medical-surgical intensive care, neurosurgical intensive care, surgical intensive care, pediatric intensive care, and non-intensive care inpatient areas [6]. Vancomycin would be completely lost as an effective antimicrobial agent in healthcare facilities, if VISA or VRSA were to become more prevalent with an increasing presence

comparable to HA-MRSA. Second, there are very few antimicrobial agents available beyond vancomycin that are effective in treating vancomycin-resistant infections. HA-MRSA is already multi-resistant to a large number of the older antimicrobial classes. The limited list of new agents available to treat vancomycin-resistant infections includes only linezolid, quinupristin-dalfopristin, daptomycin, and tigecycline. These drugs are sometimes not tolerated well by patients and issues of toxicity play a role in limiting length of therapy. Resistance to *S. aureus* has already been reported in three of these four antimicrobials and was often acquired within a short time frame of therapy use. Bringing an antibiotic to market from inception to sales is very costly for pharmaceutical companies and the incentive for focus on antibiotic production is not prominent. As a result, there is limited research and development being conducted for new antimicrobials, and therefore little promise for new antimicrobial agents in the near future. From 1997-2006, nineteen VISA cases were reported and confirmed in the U.S., four of these cases were identified in Michigan. From 2002-2006, seven VRSA cases were reported and confirmed in the U.S., five of these cases were identified in Michigan. Two additional VRSA cases were identified in Michigan in 2007. All of the VRSA cases were epidemiologically unrelated and have been confirmed by molecular testing to be unique organisms.

Surveillance for MRSA Cases

Information about MRSA and the existing differences between HA-MRSA and CA-MRSA derives from both data collected through surveillance of these organisms and through planned research investigations. There are only a limited number of population-based studies that provide detailed information on the differences between HA- and CA-

MRSA. The reasons include limited availability of funding, the difficulty in tracking large numbers of HA-MRSA in hospitals, and the difficulty identifying CA-MRSA from community settings. There are also those that believe the prevalence of MRSA is too high, so it would be impossible to control, and therefore is not beneficial to research any further. In the place of planned studies, analysis of surveillance data can be a very effective and efficient way to investigate pathogen characteristics, populations affected, risk factors, and behaviors for a specific infection type or disease. Specific data is collected, analyzed, and disseminated through surveillance. Public health surveillance is developed to provide the information needed to control and prevent disease in the population. In order to understand and control communicable diseases, the state health department maintains a list of diseases that healthcare providers and laboratories are required to report when a case is identified. The data from these reportable diseases allow staff to monitor the health of the community and provide the basis for development of education, treatment, prevention, and control efforts. The CDC's nationally notifiable disease reporting system provides a strong foundation of reporting and surveillance for pathogens posing a significant morbidity and mortality threat, providing good descriptive data from throughout the nation. State health departments also maintain reportable disease surveillance systems. Often the lists of diseases include those on the national notifiable list, in addition to diseases that may be of specific importance to the population of the state and its geographic area. Unfortunately, MRSA is neither a nationally notifiable disease nor a Michigan mandated reportable disease. The sheer number of HA-MRSA infections that have been identified in healthcare facilities for many years makes it difficult, costly, and time-consuming to conduct routine surveillance on this organism.

A good surveillance system should be simple to use, accepted by those required to report, and have a high level of sensitivity for the disease under surveillance [55]. In the case of HA-MRSA, these system attributes cannot be met. It would not be simple, but a very difficult process to collect case specific demographics and risk factor data for entry into a surveillance system, because of the high numbers of MRSA infections in healthcare systems. This method of surveillance has previously been presented for consideration at the both the national and state level, including in Michigan, and has not been accepted by the groups that would be required to do this reporting. In addition, the high prevalence of HA-MRSA would mean that many cases would most likely go unidentified and/or unreported, and this would greatly reduce the sensitivity of the surveillance system. The definition of CA-MRSA makes it a difficult candidate for surveillance. CA-MRSA occurs in the community, often among mostly healthy individuals. It would require those doing the reporting to be knowledgeable about MRSA and the risk factors of the two types, in order to accurately distinguish between HA-MRSA and CA-MRSA and to accurately identify the less established community risk factors for the infected individual. This would drastically decrease the predictive value positive of the surveillance system [55].

The Council of State and Territorial Epidemiologists (CSTE) considered a proposal in 2003 to make MRSA a notifiable condition in the U.S., in response to the increasing numbers of HA-MRSA infections and the emergence of CA-MRSA [56]. This would have meant that state health departments would require MRSA data from the healthcare providers and laboratories in their jurisdictions via a standardized case report form and then would submit this information to the CDC. Though this proposal and the

need for MRSA surveillance data were discussed at length, it was not passed or adopted as a position statement due to the time intensive and costly burden it would have placed on those required to report this information. The final decision that emerged from the discussions was that the CDC would require MRSA surveillance from nine of its Emerging Infections Program (EIP) sites (CA, CO, CT, GA, MD, MN, NY, OR, TN) through the ABCs system. These sites received considerable funding allowing them to conduct surveillance (including for MRSA) that most other state health departments could not handle due to lack of resources, staff and money. The additional recommendation was that each state consider conducting its own MRSA surveillance to the level and extent possible. The CDC conducted a survey in 2005 to collect information on the status of MRSA surveillance in the states. Beyond the nine EIP sites, little was being done. Six states (LA, MA, ME, MI, MO, WA) reported aggregate antibiogram data, and only a few additional sites reported active/passive MRSA surveillance [57]. Recently, there has been an escalation of state legislative mandates that will increase the reporting of MRSA in the near future.

The Michigan Department of Community Health (MDCH) chose to collect MRSA data via two methods, in response to the CSTE and CDC recommendations that states conduct MRSA surveillance. Antibiogram data was requested from hospital laboratories throughout Michigan beginning in 2002. These data were aggregated, analyzed, and reported yearly. The information included regional and statewide prevalence of MRSA, but was limited by only including a total percent of susceptible isolates from all isolates tested in a hospital laboratory. No specific patient or isolate information was provided [51]. To collect more specific MRSA data, MDCH conducted

surveillance for MRSA from October 1, 2004 through December 31, 2005 under a designated medical research project. This designation recognized the importance and necessity of the data and allowed for its submission to MDCH under HIPAA (Health Insurance Portability and Accountability Act) coverage without adding MRSA to the permanent Michigan reportable disease list. The caveat was that this surveillance could not be made mandatory under the medical research project designation, so submission of information was voluntary. The purpose was to collect data from both HA-MRSA and CA-MRSA infections to help characterize these cases in Michigan, in order to develop appropriate intervention and prevention guides, so that transmission and spread could be tempered. [See Appendix for MDCH MRSA Surveillance Case Report Form]

Surveillance for VISA and VRSA Cases

A proposal was also submitted to the CSTE committee to make VRSA infections notifiable conditions in the U.S., after the first case was identified in 2002. This proposal was accepted and adopted as a position statement in 2003 [58]. Under this position statement, a state would make it mandatory for all VISA and VRSA cases to be reported to its state health department and these cases would then be reported to the CDC. Most state health departments adopted this requirement and made these cases reportable from the healthcare providers and laboratories within their states. MDCH followed this recommendation and had VISA and VRSA cases added to the reportable disease list in Michigan.

The burden of reporting these cases is low by number, because only a few cases have been identified nationally to date (19 VISA cases and 9 VRSA cases). It is the response and follow-up for these cases that requires a great amount of time and effort. It

is necessary, in each case, to evaluate the patient's defined treatment regimen for effectiveness, assess infection control precautions and procedures for appropriateness, and conduct an extensive contact investigation to assure no transmission. There is an important need to identify and understand the similarities and differences between these cases, because of the significant impact they have on public health. We need to understand the patients' histories and risk factors, the infection control practices surrounding them, and the therapy regimens that have been used to treat their infections, in order to prevent future infections from emerging and being transmitted,.

Future Considerations for MRSA, VISA, and VRSA

S. aureus can be found all around us and is a part of our public health history. This organism has created mechanisms to evade our antimicrobial agents, since their initial discovery. It will continue to evolve for its own survival. Based on current indications, the incidence and prevalence of MRSA will continue to rise. The risk groups and environments for HA-MRSA and CA-MRSA will intermix and soon the distinctions between the two may become blurred. The current epidemiology must be clearly defined and understood, so that the changing epidemiology can be tracked and described appropriately. Without this knowledge, effective intervention and prevention programs cannot be developed or implemented. We need evidence-based educational messages and control measures to keep transmission of this organism in check.

Although the total number of reported VISA and VRSA cases currently remains low, new infections continue to be identified. The number of cases confirmed in Michigan has already raised concern. The dynamics of these cases must be defined and understood, so that further occurrences can be controlled and the possibility for

transmission prevented. The serious threat of losing vancomycin as an effective antimicrobial agent increases as the number of VISA and VRSA cases climbs, taking us closer to the end of our current antibiotic lifeline.

Purpose of the Research

MRSA, VISA, and VRSA infections present differently in communities throughout the United States. It is imperative that a variety of areas continue to conduct individual efforts to track and characterize these organisms, in order to control the burden that they place on specific individuals, healthcare systems, and communities.

The research presented in the following chapters utilizes Michigan MRSA surveillance data to address the issue of accurately identifying an MRSA infection as healthcare- or community-associated, and to appropriately characterize the MRSA infections in Michigan and the VRSA infections in the nation. The investigation in Chapter II uses the dataset to evaluate the concordance in classification results when MRSA infections are defined as healthcare- or community-associated using three preexisting classification schemes. The analyses in Chapter III use a subset of the Michigan MRSA infection data, which have PFGE results available, to identify a more accurate model to define MRSA infections as healthcare- or community-associated. The examination in Chapter IV utilizes the newly identified model, and PFGE result when it is available, to classify the complete dataset of Michigan MRSA infections as healthcare- or community-associated and to present the profile and characterization of these Michigan cases. The report in Chapter V presents the clinical characteristics, epidemiologic investigations, infection control evaluations, and microbiologic findings of the seven VRSA cases identified in the U.S. from 2002-2006. The findings from this

research will provide important information to public health professionals, healthcare providers, and researchers for the accurate identification of HA-MRSA, CA-MRSA, and VRSA. This accuracy is pertinent to the effective treatment, appropriate infection control strategies, and targeted prevention efforts of these very relevant organisms. These investigations have been approved by the Institutional Review Boards of the Michigan Department of Community Health and the University of Michigan.

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Chapter II

Potential for Misclassification in Defining Methicillin-Resistant *Staphylococcus aureus* Infections as Healthcare- or Community-Associated by Healthcare Risk Factor, Infection Type, or Susceptibility Pattern

Abstract

Background: Healthcare providers and researchers utilize a variety of methods to classify methicillin-resistant *Staphylococcus aureus* (MRSA) infections as either healthcare-associated (HA) or community-associated (CA). The method chosen is often dependent upon the information available to them. The results of that classification may dictate patient treatment, infection control recommendations, and prevention efforts. This investigation defines MRSA infections reported from throughout Michigan as either HA or CA using three common classification schemes: healthcare risk factor, infection type, and susceptibility pattern, and then examines the results for concordance/discordance across the three classifications.

Methods: MRSA infections were voluntarily reported in Michigan to the Michigan Department of Community Health (MDCH) between October 1, 2004 and December 31, 2005. Data on patient demographics, risk factors, and infection information were collected on the MDCH MRSA Surveillance Case Report Form and submitted to MDCH with laboratory susceptibility test results. A total of 2,151 reported cases were used in the analyses.

Results: MRSA infections were first defined as HA or CA, according to each classification scheme separately: healthcare risk factor, infection type, and susceptibility

pattern. The demographic, clinical, and microbiologic variables showed similar distributions within the HA or CA categorizations among the three classification methods. These results are consistent with previously published literature according to the differing presentations of HA- and CA-MRSA. However, when the HA or CA results across the three classification schemes were compared for each case, a large proportion of cases (42%) had discordant results.

Conclusion: This investigation shows that due to the high level of disagreement between the classification methods, decisions made for patients and study results are dependent upon the method used. Further research is needed to find a more accurate and consistent way to classify MRSA infections, prevalent throughout Michigan and elsewhere, as HA or CA.

Introduction

Staphylococcus aureus is a human commensal organism and has the ability to colonize an individual for short or extended periods of time [1-3]. It is an opportunistic pathogen and has long been known as a common cause of human infections. These infections range from minor dermatological conditions like small pustules (i.e. pimples), furuncles (i.e. boils), and folliculitis to serious systemic illnesses, like osteomyelitis, pneumonia, and bacteremia.

Methicillin, first introduced in 1960, was one of the earliest antibiotics used to treat *S. aureus* infections in response to growing numbers of *S. aureus* isolates resistant to penicillin. The first cases of methicillin-resistant *S. aureus* (MRSA) were reported from the United Kingdom shortly thereafter [4]. Hospitals in the United States began reporting an increase in MRSA in the mid-1970s. The incidence of MRSA grew steadily and by the 1990s, MRSA was considered endemic in large, urban medical centers in the U.S. [5-10]. Concurrently, the first reports of MRSA identified in community settings were published in the early 1980s [11-14].

It became evident, as MRSA case reports increased from both healthcare and community settings, that cases occurring in these two distinct settings were different epidemiologically. It was found that these two types of MRSA infections usually occur among individuals with different health risk factors and in separate age groups. They present as different types of infections, with varying resistance patterns to therapeutic drugs [15-24]. These differences relate to how and why an individual acquires infection, their potential for transmission, the seriousness of the infection, consequences to the patient, effective treatment options, and costs relative to all of these factors [25, 26].

Because of these differences, health professionals have distinguished between these two types of MRSA infections by referring to them as either healthcare-associated MRSA (HA-MRSA) or community-associated MRSA (CA-MRSA) [27-29].

Molecular testing is often used as a gold standard for distinguishing amongst MRSA types. There are, however, three common and less resource intensive ways that HA-MRSA and CA-MRSA are differentiated: by healthcare risk factor, infection type, and susceptibility pattern [30-38]. These three classification schemes are used by healthcare providers and researchers and have proven useful in categorizing MRSA infections as HA-MRSA or CA-MRSA for both patients and study participants [27, 39-50]. Healthcare risk factor may be the most preferred classification method, however this information is the most difficult to collect with a high level of accuracy. The choice of classification method is ultimately left to the discretion of the investigator or clinician and is dependent upon the data that is available. The results achieved using the three most common classification methods have never been systematically compared and published in the peer review literature. If a high level of inconsistency in categorization exists depending on which of the three classification methods is utilized then study results and decisions made for patients would largely depend upon the method used, and would vary by classification scheme.

In this study, we define and characterize MRSA infections reported in Michigan as either HA or CA based upon each of the three classification schemes: healthcare risk factor, infection type, and susceptibility pattern. We then compare and contrast the three sets of results in order to assess the level of concordance/discordance using the three different classifications.

Methods

Data Source

MRSA surveillance was conducted by the Michigan Department of Community Health (MDCH) from October 1, 2004 through December 31, 2005. Surveillance was carried out as a designated medical research project for public health purposes, which permits collection of data of public health significance without having to revise the reportable disease list to make this reporting mandatory. This allows for more specific data from both HA-MRSA and CA-MRSA infections to be collected to help epidemiologically characterize these cases in Michigan. The data submission for individual MRSA cases under this designation is voluntary, although the reporting of MRSA *outbreaks* is mandatory by law in Michigan. This research project was approved by the MDCH Chief Medical Executive and the MDCH Human Subjects Committee, as well as the University of Michigan Institutional Review Board. The request to report individual MRSA cases to MDCH was announced statewide via letters, updates to reporting guidelines, and presentations to healthcare providers, laboratories, and local health departments throughout the state. Individual cases of MRSA infection were voluntarily reported through local health departments to the MDCH Antimicrobial Resistance Epidemiologist. Information was submitted using a two-page MDCH MRSA Surveillance Case Report Form and laboratory susceptibility test result sheets.

A total of 2,227 unduplicated MRSA cases were reported by private physicians, correctional facilities, infection control professionals, hospital laboratories, and local health departments throughout Michigan from October 1, 2004 through December 31, 2005. Seventy-six cases were deleted during data cleaning procedures due to: non-

Michigan residence (n=19) and infection type specified as none (n=54) or colonization (n=3). The dataset used for the analyses contained 2,151 unique MRSA infections among Michigan residents.

Data Management

All cases in the dataset were defined as either HA-MRSA or CA-MRSA, three separate times based upon the three different classification schemes: healthcare risk factor, infection type, and susceptibility pattern.

Classified by healthcare risk factor

Cases were labeled as HA-MRSA on the basis of healthcare risk factor if they had at least one of the following established risk factors: were hospitalized >48 hours prior to the current infection (i.e., patient was not MRSA-infected at time of hospitalization but culture and infection were identified > 48 hours after admission), were in an intensive care unit (ICU) >48 hours prior to the current infection, were hospitalized in the previous year (i.e., admitted and discharged from a hospital at any time during the year prior to the current infection), had surgery in the previous year, received dialysis in the previous year, had a percutaneous device or indwelling catheter in the previous year, or if they resided in a long-term care (LTC), nursing home or rehabilitation facility in the previous year [40, 51, 52]. Cases with "no" reported for all seven HA-MRSA risk factors (i.e., had none of the established risk factors) were considered CA-MRSA by default.

Classified by infection type

Cases were labeled as CA-MRSA on the basis of infection type if a skin or soft tissue infection was diagnosed, including abscess, cellulitis, folliculitis, and impetigo, or if a wound infection had "skin" identified as the culture site. Cases with other and more

serious infections, including bacteremia, meningitis, osteomyelitis, pneumonia, septic arthritis, and surgical site infection were labeled as HA-MRSA. CA-MRSA can in some situations, cause more serious infections like pneumonia or bacteremia, but these infections are more typically caused by HA-MRSA and are usually accompanied by the HA-MRSA risk factors listed previously [29, 46]. Therefore, if a case had both a skin or soft tissue infection and more invasive infection concurrently, it was considered HA-MRSA to give more weight to the more serious infection type. Only thirteen cases met this criterion with either skin/soft tissue infection and bacteremia (n=8) or skin/soft tissue infection and pneumonia (n=5) present simultaneously.

Classified by susceptibility pattern

Cases were labeled as CA-MRSA on the basis of susceptibility pattern if their isolates were resistant only to β-lactams, including cephalosporins and carbapenems. This is the basic resistance pattern that defines MRSA [53]. Cases were labeled as HA-MRSA if resistance to additional antimicrobial classes beyond β-lactams, including cephalosporins and carbapenems, was also reported. This higher resistance included, but was not limited to, aminoglycosides, folate pathway inhibitors, lincosamides, fluoroquinolones, and tetracyclines. Erythromycin, a macrolide, was not used in the susceptibility pattern categorization, based on research showing increased CA-MRSA resistance to erythromycin [33, 43, 54] and the large overall proportion of erythromycin-resistance in this Michigan dataset.

Data Analysis

The 2,151 MRSA infection cases included in this study were categorized as HA-MRSA or CA-MRSA three separate times, based upon each of the three classification

schemes described above: healthcare risk factor, infection type, and susceptibility pattern. Univariate analyses were conducted for each of the three classifications to provide a comparison of demographic and clinical patterns of HA-MRSA versus CA-MRSA infections in Michigan. Frequencies, percentages, and distributions of HA-MRSA versus CA-MRSA infections are reported for each of the three classification methods by gender, race, age, hospitalized during time of MRSA infection, survival during time of MRSA infection, preexisting medical conditions, type of infection, healthcare risk factors, and susceptibilities to specific antimicrobial agents. Chi-square and Fisher's exact tests (when expected cell frequencies were <5) were performed on categorical variables to test for significant differences in proportions between HA-MRSA and CA-MRSA defined cases. The t-test was used to make the comparison between HA-MRSA and CA-MRSA cases for the continuous age variable. Results of the MRSA categorizations by the three classifications are then compared for each case and the overall concordance/discordance of results determined. Results were considered statistically significant if the p-value was <0.05. All statistical analyses were conducted using SAS® statistical software (SAS System for Windows V9.1.3, SAS Institute Inc., Cary, NC).

Results

Of the total 2,151 cases analyzed in this investigation, 1,188 (55%) were male and the mean age of all cases was 44 years old (s.d.=25 years). The race/ethnicity distribution was as follows: 1,293 (60%) white, 382 (18%) black, 81 (4%) "other" (i.e., Hispanic/Latino, American Indian/Alaskan Native, Asian, or Native Hawaiian/Pacific Islander), and 395 (18%) unknown. Among all cases, 739 (34%) were hospitalized

during time of MRSA infection, 80 (4%) died during time of MRSA infection, 1,338 (62%) had at least one preexisting illness reported, while 315 (15%) were reported as having no preexisting illnesses and 498 (23%) were reported as unknown.

Classified by healthcare risk factor

Statistically significant results from the categorization of MRSA (HA or CA) by healthcare risk factor are presented in Table 2.1. According to this classification, 37% of cases are HA-MRSA and 63% are CA-MRSA. A greater proportion of males had CA-MRSA infections than females, while the distribution was almost equal in the HA-MRSA group ($p=0.005$). The higher proportion of whites was in the HA-MRSA group, but the higher proportion of blacks was in the CA-MRSA group ($p=0.009$). The mean age for HA-MRSA infections was 58 years old (s.d.=23 years), and for CA-MRSA was 35 years old (s.d.=21 years) ($p<0.0001$). The highest proportions of HA-MRSA infections occurred among those 50 years and older, while the highest proportions of CA-MRSA infections occurred among those younger than 50 years old ($p<0.0001$) (Figure 2.1). Sixty-two percent of the individuals with HA-MRSA infections were hospitalized, while 22% with CA-MRSA were hospitalized during time of MRSA infection ($p<0.0001$). Of the individuals with HA-MRSA, 10% died during time of MRSA infection compared to only 1% with CA-MRSA ($p<0.0001$). HA-MRSA infected individuals suffered from more preexisting illnesses than those with CA-MRSA, including diabetes mellitus, chronic renal insufficiency, dialysis, cardiovascular disease, coronary heart failure, chronic obstructive pulmonary disease, and overall "any" preexisting illness (for each illness, $p<0.0001$). Of the five most common infection types of those investigated, individuals with CA-MRSA were most likely to have skin/soft tissue infections

($p<0.0001$), while those with HA-MRSA suffered from bacteremia, pneumonia, and surgical site infections (for each infection type, $p<0.0001$). The proportion of individuals with "wound" infections did not differ significantly between the HA- and CA-MRSA groups ($p=0.363$), most likely due to the vagueness of this term, which is generically used to describe infections in both healthcare and community settings. Of the non-β-lactam drugs evaluated, the HA-MRSA infected group was more likely to be resistant to ciprofloxacin, clindamycin, gentamicin, levofloxacin, and trimethoprim-sulfamethoxazole (for each drug, $p<0.0001$) compared to the CA-MRSA group.

Classified by infection type

Statistically significant results from the categorization of MRSA (HA or CA) by infection type are presented in Table 2.2. According to this classification, 39% of cases are HA-MRSA and 61% are CA-MRSA; 393 cases are unknown due to missing infection type data. A greater proportion of males had CA-MRSA infections than females, while the distribution was almost equal in the HA-MRSA group ($p=0.0003$). The higher proportion of whites was in the HA-MRSA group, but the higher proportion of blacks was in the CA-MRSA group ($p<0.0001$). The mean age for HA-MRSA infections was 60 years old (s.d.=23 years), and for CA-MRSA was 35 years old (s.d.=20 years) ($p<0.0001$). The highest proportions of HA-MRSA infections occurred among those 50 years and older, while the highest proportions of CA-MRSA infections occurred among those younger than 50 years old ($p<0.0001$) (Figure 2.2). Sixty-six percent of the individuals with HA-MRSA infections were hospitalized, while 23% with CA-MRSA were hospitalized during time of MRSA infection ($p<0.0001$). Of the individuals with HA-MRSA, 11% died during time of MRSA infection compared to only 1% with CA-

MRSA ($p<0.0001$). HA-MRSA infected individuals suffered from more preexisting illnesses than those with CA-MRSA, including diabetes mellitus, chronic renal insufficiency, dialysis ($p=0.0006$), cardiovascular disease, coronary heart failure, chronic obstructive pulmonary disease, and overall "any" preexisting illness (for each illness not previously specified, $p<0.0001$). Those with HA-MRSA infections were more likely to have: been hospitalized >48 hours prior to the current infection, in ICU >48 hours prior to the current infection, hospitalized in the previous year, had surgery in the previous year, received dialysis in the previous year, had a percutaneous device or indwelling catheter in the previous year, and/or resided in a LTC, nursing home or rehabilitation facility in the previous year compared to those with CA-MRSA (for each risk factor, $p<0.0001$). Of the non-β-lactam drugs evaluated, the HA-MRSA infected group was more likely to be resistant to ciprofloxacin, clindamycin, gentamicin, levofloxacin, and trimethoprim-sulfamethoxazole (for each drug, $p<0.0001$) compared to the CA-MRSA group.

Classified by susceptibility pattern

Statistically significant results from the categorization of MRSA (HA or CA) by susceptibility pattern are presented in Table 2.3. According to this classification, 54% of cases are HA-MRSA and 46% are CA-MRSA; 63 cases are unknown due to missing susceptibility pattern data. A greater proportion of males had CA-MRSA infections than females, while the distribution was more equal in the HA-MRSA group ($p=0.007$). The higher proportion of whites was in the HA-MRSA group, but the higher proportion of blacks was in the CA-MRSA group ($p<0.0001$). The mean age for HA-MRSA infections was 54 years old (s.d.=24 years), and for CA-MRSA was 32 years old (s.d.=19 years)

($p<0.0001$). The highest proportions of HA-MRSA infections occurred among those 40 years and older, while the highest proportions of CA-MRSA infections occurred among those younger than 40 years old ($p<0.0001$) (Figure 2.3). Fifty-one percent of the individuals with HA-MRSA infections were hospitalized, while 22% with CA-MRSA were hospitalized during time of MRSA infection ($p<0.0001$). Of the individuals with HA-MRSA, 8% died during time of MRSA infection compared to only 1% with CA-MRSA ($p<0.0001$). HA-MRSA infected individuals suffered from more preexisting illnesses than those with CA-MRSA, including diabetes mellitus, chronic renal insufficiency, dialysis, cardiovascular disease, coronary heart failure, chronic obstructive pulmonary disease, and overall "any" preexisting illness (for each illness, $p<0.0001$). Those with HA-MRSA infections were more likely to have: been hospitalized >48 hours prior to the current infection, in ICU >48 hours prior to the current infection, hospitalized in the previous year, had surgery in the previous year, received dialysis in the previous year, had a percutaneous device or indwelling catheter in the previous year, and/or resided in a LTC, nursing home or rehabilitation facility in the previous year compared to those with CA-MRSA (for each risk factor, $p<0.0001$). Of the five most common infection types of those investigated, individuals with CA-MRSA were most likely to have skin/soft tissue infections ($p<0.0001$), while those with HA-MRSA suffered from bacteremia, pneumonia, and surgical site infections (for each infection type, $p<0.0001$). The proportion of individuals with "wound" infections did not differ significantly between the HA- and CA-MRSA groups ($p=0.638$), most likely due to the vagueness of this term, which is generically used to describe infections in both healthcare and community settings.

Concordance Analysis

Results from the concordance/discordance analysis are shown in Table 2.4 and reveal that of the 2,151 cases, 427 (20%) cases are consistently defined as HA-MRSA infections by all three classifications, while 548 (25%) cases are consistently defined as CA-MRSA infections by all three classifications. Of the total cases, 897 (42%) are not consistently defined by the three different classifications. Of these discordant cases, 292 are defined as HA-MRSA by two classifications and CA-MRSA by a third classification, 437 are defined as CA-MRSA by two classifications and HA-MRSA by a third classification, and 168 are defined as HA-MRSA by one classification, as CA-MRSA by a second classification, and are missing results that could not be calculated for a third classification. There are 279 (13%) cases where concordance/discordance results could not be fully determined by all three classifications because of incomplete case data. Of these cases, 68 are defined as HA-MRSA by two classifications and are missing data necessary to categorize by the third classification method, 202 are defined as CA-MRSA by two classifications with missing data for the third classification, and finally, a small number of cases (i.e., 2 cases of HA-MRSA and 7 cases of CA-MRSA) had only sufficient data to categorize based on a single classification. Missing data in Table 2.4 is due to unknown infection type in 393 (18%) of the total case population (Table 2.2), and unknown susceptibility pattern in 63 (3%) of the total case population (Table 2.3). Nine cases have missing data for both infection type and susceptibility pattern.

Discussion

MRSA infections in this dataset are defined as HA or CA by the classification schemes: healthcare risk factor, infection type, and susceptibility pattern (Tables 2.1-2.3). The demographic, clinical, and microbiologic variables showed similar distributions within the HA and CA categorizations among the three classification methods, and are consistent with those seen in previously published literature, according to the differing presentations of HA- and CA-MRSA [30-38]. The HA-MRSA group encompasses individuals who are at greater risk for becoming infected by this opportunistic pathogen because they unwittingly present the opportunity. These individuals are generally older, have chronic underlying illnesses, and require more frequent interactions with healthcare facilities, all of which predispose them to more serious and resistant infections. The CA-MRSA group includes individuals who, in general, are otherwise healthy. They are usually not predisposed by age or underlying illness to these infections, but by specific activities and community interactions that place them at an increased risk for acquisition. In this study population, the proportion of males and the proportion of blacks with CA-MRSA infections were higher compared to their HA-MRSA counterparts. Studies have shown that a higher percentage of men are more likely to engage in "close contact" sports, have more cuts and skin abrasions, and live in close congregate settings like military barracks or correctional facilities, all previously established risk factors for CA-MRSA [18, 23, 24]. Studies have also reported a higher prevalence of CA-MRSA infections among males in urban settings, men who have sex with men, and drug users [3, 41, 55-59].

It would appear that all three classifications are accurate, yield very similar results, and could be used interchangeably to define an MRSA infection as HA or CA, based on the consistent distributions of descriptive variables within the HA and CA categories for each of the three classification methods. A discrepancy between these three methods is first seen when comparing the overall proportions of HA versus CA cases within each of the classifications; these distributions are similar for healthcare risk factor and infection type, but are notably different for susceptibility pattern. Additional analysis reveals concordance across all three classifications for only 975 (45%) of the cases (Table 2.4). 897 (42%) of the cases are consistently defined as HA or CA based on two of the classifications, but not the third. The remaining 279 (13%) cases are missing data that prevent comparison of all three classification methods.

The large number of discordant cases, 897 or 42% of the total MRSA cases reported, are of concern with regard to defining MRSA infections as HA or CA. These results indicate that the classification of a case as HA or CA is dependent on the method chosen. Healthcare risk factor is the inconsistent result for 223 of the cases, infection type is the inconsistent result for 177 of the cases, and susceptibility pattern is the inconsistent result for 329 of the cases. Each of the three classification methods is inconsistent with the other two, for a number of cases, so it is not possible to identify one method as the most accurate. These noted inconsistencies are somewhat inherent, because each classification scheme defines an MRSA infection using a different characteristic; one considers healthcare interactions of the patient, the second the presentation of infection, and the third the genetic makeup of the pathogen. Each piece of information is important, but alone lacks the full picture. The three pieces of

information together would provide a more complete picture of the MRSA infection; how it was acquired, how it presented, and the specific makeup of the pathogen. This is important as MRSA is continually evolving and some studies indicate that the settings for HA and CA infections may have begun to overlap. These results suggest that further investigation is needed and analyses should be conducted to search for a more reliable combination of variables that can be used to define MRSA infection as either HA or CA. This new combination may or may not include the three currently utilized classification schemes of healthcare risk factor, infection type, and susceptibility pattern. In addition, other variables should be considered, including age, hospitalization, survival, and preexisting illness.

There are some limitations to this categorization investigation. Data were abstracted from medical chart reviews, not patient interviews, therefore information on healthcare risk factors and preexisting illnesses may not be all inclusive. The data were, however, complete for all seven healthcare risk factors with either a "yes" or "no" answer submitted. There are also missing data for some of the demographic, infection type, and susceptibility pattern variables. A more complete and accurate dataset would strengthen the results and help to determine the concordance/discordance for the remaining 13% of cases, but the proportion of cases missing data was low compared to the data obtained from the large number of cases reported. And from the available data, a large number of categorizations were shown to be discordant (42%). The outcomes for hospitalization and survival were not strictly due to MRSA, though these variables do represent seriousness of illness and serve as proxies during the same time frame as the MRSA infection. These data may not provide a true representative sample of the proportion of

HA- and CA-MRSA infections throughout Michigan, because this surveillance was voluntary. The data that were collected do provide the necessary case and variable distributions to address the goal of this investigation; to categorize by the three classification methods and test for concordance/discordance.

In conclusion, the data on MRSA infections submitted from throughout Michigan for a 15 month period provided reliable information from a variety of sources and patients. The 2,151 cases used in these analyses offered a broad range of MRSA infections among individuals with varying demographics and health risk factors. This investigation showed that the relationship between MRSA categorization (HA or CA) and a variety of demographic and health-related covariates were similar across classification method. Defining MRSA infections as either HA or CA by healthcare risk factor, infection type, or susceptibility pattern yielded similar proportions by the first two criteria (37% and 39% HA, respectively), but more HA classification (54%) using the third criterion. Given that the three criteria reflect different aspects of the disease, it is not necessarily surprising that they are only modestly concordant. However, the degree of discordance among the three classification methods makes it clear that consistent comparisons cannot be made. Further investigations should consider a gold standard molecular test, like pulsed field gel electrophoresis, and other patient descriptive variables, in addition to the three classification schemes, to find a more accurate and consistent way to define MRSA infections as HA or CA. A more accurate profile of an MRSA infection allows for more appropriate messages for control of transmission and guided prevention efforts.

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Table 2.1. Michigan MRSA Infections Classified by Healthcare Risk Factor as Healthcare-Associated (HA) or Community-Associated (CA). (N=2,151)

Demographic/Characteristic	Healthcare-Associated	Community-Associated	*p*-value*
	N=805 (37%) n (%)	N=1346 (63%) n (%)	
Gender: Male	413 (51)	775 (58)	0.005
Race: White Black Other	538 (78) 127 (18) 28 (4)	755 (71) 255 (24) 53 (5)	0.009
Age: (range: 0-80+)	794 ($\bar{x}$=58 s.d.=23)	1327 ($\bar{x}$=35 s.d.=21)	<0.0001
Hospitalized: Yes	487 (62)	252 (22)	<0.0001
Survival: Died	68 (10)	12 (1)	<0.0001
Preexisting Illness(s):			
None	42 (5)	273 (30)	<0.0001
Diabetes Mellitus	259 (34)	103 (11)	<0.0001
Chronic Renal Insufficiency	112 (15)	18 (2)	<0.0001
Dialysis	41 (5)	4 (.4)	<0.0001
Cardiovascular Disease	184 (24)	61 (7)	<0.0001
Coronary Heart Failure	161 (21)	28 (3)	<0.0001
COPD	159 (21)	48 (5)	<0.0001
Any Preexisting Illness	714 (94)	624 (70)	<0.0001
Infection Type:			
Bacteremia	76 (10)	16 (2)	<0.0001
Pneumonia	152 (21)	25 (2)	<0.0001
Skin / Soft Tissue	233 (31)	841 (83)	<0.0001
Surgical Site	52 (7)	10 (1)	<0.0001
Drug Resistance:			
Ciprofloxacin	187 (75)	173 (37)	<0.0001
Clindamycin	356 (66)	200 (22)	<0.0001
Gentamicin	54 (8)	21 (2)	<0.0001
Levofloxacin	537 (77)	345 (33)	<0.0001
Trimeth.-Sulfamethoxazole	17 (2)	5 (.41)	<0.0001

*p-values shown are from χ^2 tests for categorical variables and t-test for Age.

Figure 2.1. Age Group Distribution of Michigan MRSA Infections Classified by Healthcare Risk Factor as Healthcare-Associated (HA) or Community-Associated (CA).

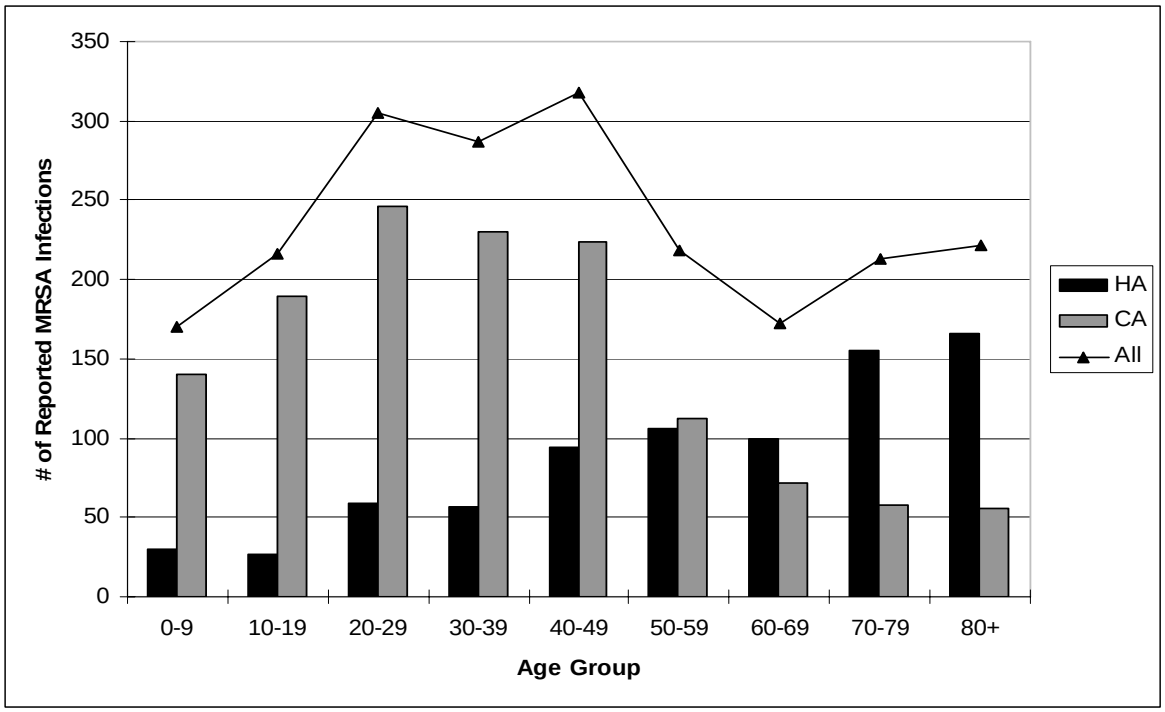

Table 2.2. Michigan MRSA Infections Classified by Infection Type as Healthcare-Associated (HA) or Community-Associated (CA). (N=1,758) (Unknown=393)

Demographic/Characteristic	Healthcare-Associated	Community-Associated	*p*-value*
	N=684 (39%) n (%)	N=1074 (61%) n (%)	
Gender: Male	351 (51)	646 (60)	0.0003
Race: White	463 (80)	604 (67)	<0.0001
Black	91 (16)	251 (28)	
Other	24 (4)	47 (5)	
Age 0-80+	678 ($\bar{x}$=60 s.d.=23)	1058 ($\bar{x}$=35 s.d.=20)	<0.0001
Hospitalized: Yes	441 (66)	238 (23)	<0.0001
Survival: Died	68 (11)	5 (1)	<0.0001
Preexisting Illness(s):			
None	34 (5)	261 (29)	<0.0001
Diabetes Mellitus	221 (34)	108 (12)	<0.0001
Chronic Renal Insufficiency	95 (15)	24 (3)	<0.0001
Dialysis	28 (4)	13 (1)	0.0006
Cardiovascular Disease	159 (24)	70 (8)	<0.0001
Coronary Heart Failure	142 (22)	28 (3)	<0.0001
COPD	156 (24)	34 (4)	<0.0001
Any Preexisting Illness	608 (95)	620 (71)	<0.0001
Healthcare Risk Factors:			
Hospitalized >48 hours	112 (16)	31 (3)	<0.0001
In ICU >48 hours	60 (9)	8 (1)	<0.0001
Hospitalized in Prior Year	345 (50)	162 (15)	<0.0001
Surgery in Prior Year	195 (29)	101 (9)	<0.0001
Dialysis in Prior Year	37 (5)	16 (1)	<0.0001
Indwell Device in Prior Yr	198 (29)	64 (6)	<0.0001
LTC/Rehab in Prior Year	204 (30)	46 (4)	<0.0001
Drug Resistance:			
Ciprofloxacin	166 (83)	121 (33)	<0.0001
Clindamycin	323 (71)	130 (18)	<0.0001
Gentamicin	49 (8)	13 (1)	<0.0001
Levofloxacin	488 (82)	260 (30)	<0.0001
Trimeth.-Sulfamethoxazole	17 (3)	4 (.42)	<0.0001

*p-values shown are from χ^2 tests for categorical variables and t-test for Age.

Figure 2.2. Age Group Distribution of Michigan MRSA Infections Classified by Infection Type as Healthcare-Associated (HA) or Community-Associated (CA).

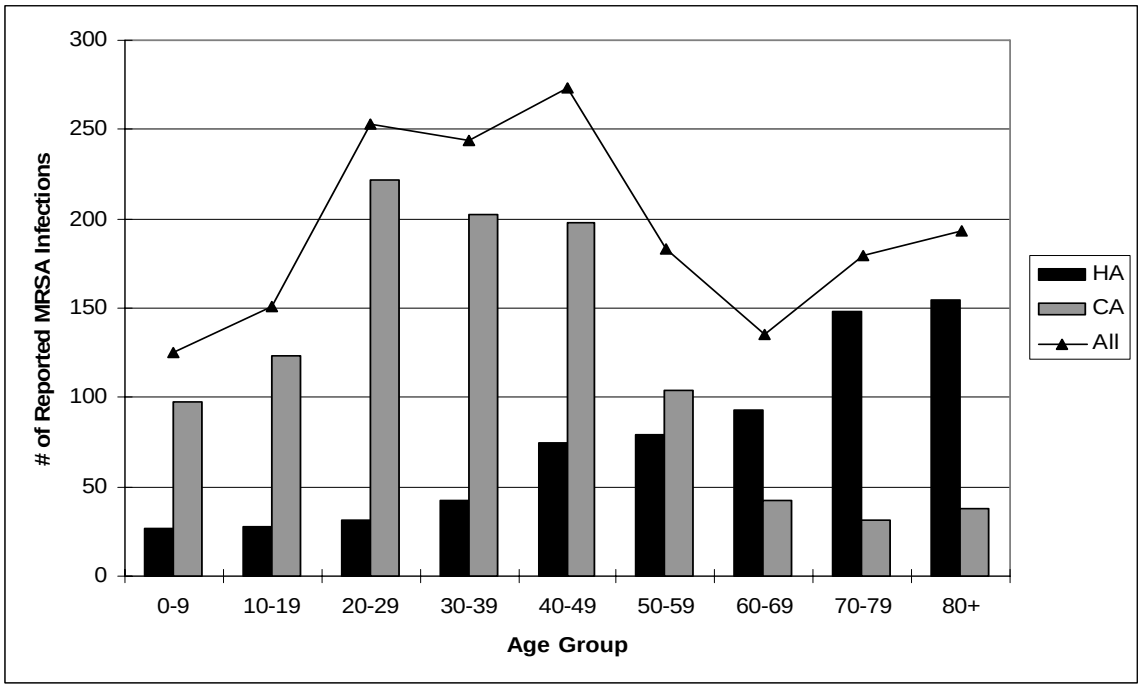

Table 2.3. Michigan MRSA Infections Classified by Susceptibility Pattern as Healthcare-Associated (HA) or Community-Associated (CA). (N=2,088) (Unknown=63)

Demographic/Characteristic	Healthcare-Associated	Community-Associated	*p*-value*
	N=1119 (54%) n (%)	N=969 (46%) n (%)	
Gender: Male	587 (52)	565 (58)	0.007
Race: White	714 (78)	531 (67)	<0.0001
Black	164 (18)	214 (27)	
Other	32 (4)	46 (6)	
Age 0-80+	1110 ($\bar{x}$=54 s.d.=24)	950 ($\bar{x}$=32 s.d.=19)	<0.0001
Hospitalized: Yes	529 (51)	181 (22)	<0.0001
Survival: Died	73 (8)	5 (1)	<0.0001
Preexisting Illness(s):			
None	101 (11)	207 (29)	<0.0001
Diabetes Mellitus	277 (30)	65 (9)	<0.0001
Chronic Renal Insufficiency	113 (12)	10 (1)	<0.0001
Dialysis	37 (4)	5 (1)	<0.0001
Cardiovascular Disease	197 (21)	36 (5)	<0.0001
Coronary Heart Failure	164 (18)	17 (2)	<0.0001
COPD	172 (19)	25 (4)	<0.0001
Any Preexisting Illness	812 (89)	481 (70)	<0.0001
Healthcare Risk Factors:			
Hospitalized >48 hours	120 (11)	26 (3)	<0.0001
In ICU >48 hours	56 (5)	11 (1)	<0.0001
Hospitalized in Prior Year	415 (37)	115 (12)	<0.0001
Surgery in Prior Year	243 (22)	69 (7)	<0.0001
Dialysis in Prior Year	44 (4)	7 (1)	<0.0001
Indwell Device in Prior Yr	216 (19)	45 (5)	<0.0001
LTC/Rehab in Prior Year	226 (20)	30 (3)	<0.0001
Infection Type:			
Bacteremia	76 (8)	14 (2)	<0.0001
Pneumonia	151 (16)	19 (2)	<0.0001
Skin / Soft Tissue	389 (42)	657 (85)	<0.0001
Surgical Site	51 (5)	9 (1)	<0.0001

*p-values shown are from χ^2 tests for categorical variables and t-test for Age.

Figure 2.3. Age Group Distribution of Michigan MRSA Infections Classified by Susceptibility Pattern as Healthcare-Associated (HA) or Community-Associated (CA).

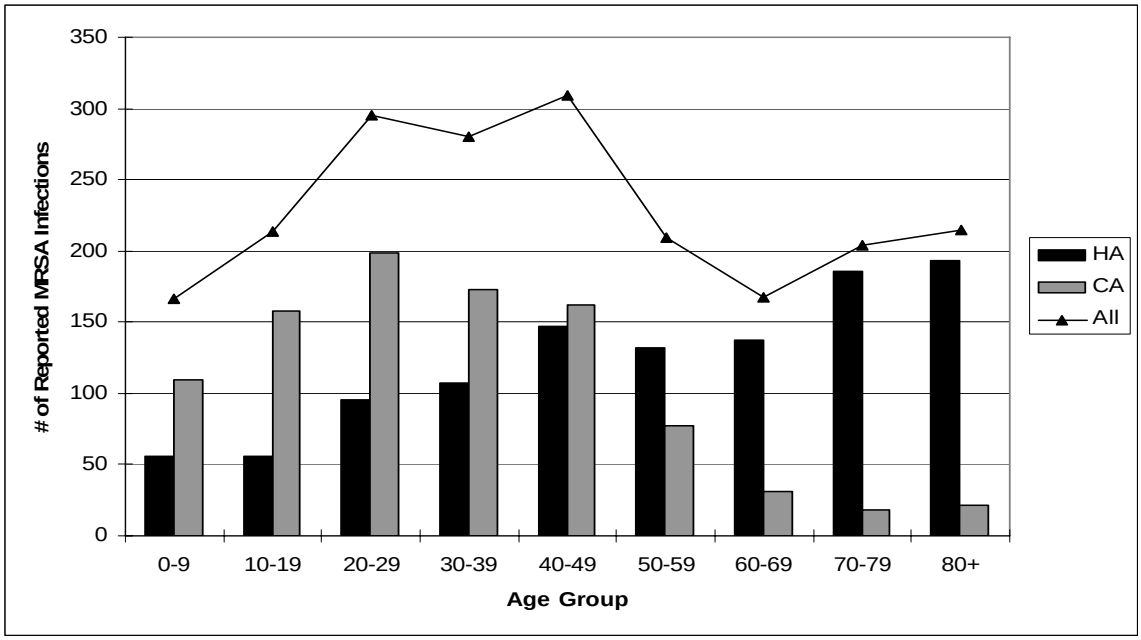

Table 2.4. Comparison of MRSA Infections Categorized by the Three Classifications (Healthcare Risk Factor, Infection Type, Susceptibility Pattern) as Either Healthcare-Associated (HA=1) or Community-Associated (CA=0).

	Healthcare Risk Factor Results	**Infection Type Results**	**Susceptibility Pattern Results**	**# of Cases Matching Row Combination Results [n, %]**
Concordant	1	1	1	427 (20)
	0	0	0	548 (25)
			Total:	**975 (45%)**
Discordant	1	1	0	59 (3)
	1	0	1	119 (5)
	0	1	1	114 (5)
	0	0	1	270 (13)
	0	1	0	58 (3)
	1	0	0	109 (5)
	1	0	.	5 (.2)
	1	.	0	16 (.7)
	0	1	.	4 (.1)
	0	.	1	143 (7)
			Total:	**897 (42%)**
Unable to Determine	1	1	.	22 (1)
	1	.	1	46 (2)
	1	.	.	2 (.5)
	0	0	.	23 (1)
	0	.	0	179 (8)
	0	.	.	7 (.5)
			Total:	**279 (13%)**
			Total:	**2,151 (100%)**

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Chapter III

A Proposed New Multivariable Model to Define Methicillin-Resistant *Staphylococcus aureus* Infections as Healthcare- or Community-Associated

Abstract

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are often defined as healthcare- (HA) or community-associated (CA) using one of three classification schemes: healthcare risk factor, infection type, or susceptibility pattern. All three of these methods have been shown to produce discordant results when compared. A fourth method utilized for the classification of MRSA as HA or CA is laboratory molecular typing. This investigation uses pulsed-field gel electrophoresis (PFGE) test result as a gold standard against which an entirely new classification method will be compared. Development of the new classification method considered the three commonly used classification variables along with other important contributing variables simultaneously, in order to improve categorization of an MRSA infection as HA or CA.

Methods: A dataset of 2,151 MRSA infections in Michigan were voluntarily reported to the Michigan Department of Community Health (MDCH) between October 1, 2004 and December 31, 2005. Patient demographic, risk factor, and infection information was recorded on the MDCH MRSA Surveillance Case Report Form and submitted to MDCH along with laboratory susceptibility test results. A subset

of 244 MRSA infections with available PFGE results were analyzed to find the best set of predictors of the PFGE result. Logistic regression was used and results were presented as sensitivity/specificity, predictive value, and receiver operating characteristic (ROC) curves.

Results: The identified logistic regression model was better able to predict the PFGE classification as HA or CA (Max-rescaled $R^2 = 61\%$) then any of the currently used classification methods: healthcare risk factor, infection type, or susceptibility pattern (Max-rescaled $R^2 = 21\%$, 34%, 46%, respectively). The variables in the best logistic model were infection type, susceptibility pattern, age, and hospitalized during the time of MRSA infection.

Conclusion: This investigation has established an improved method to categorize MRSA infections as HA or CA using a combination of predictor variables. The improved accuracy will better target appropriate prevention and intervention efforts.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been a common cause of human infections in the Unites States in both the healthcare and community settings since the 1980s [1-6]. Epidemiologically, MRSA infections present differently in these two settings in persons of varying age groups and with different health risk factors [7-9]. Clinically, these organisms cause a broad range of infection types that require varying treatment modalities [10-13]. The numbers of MRSA infections in both the healthcare and community settings continue to rise and can pose a significant morbidity and mortality risk to those who are infected. Therefore, understanding and being able to differentiate between healthcare and community MRSA strains is important for the improvement of targeted public health and infection control prevention and intervention strategies.

Laboratory molecular strain typing methods have proved invaluable in tracking and characterizing the organisms that cause MRSA infections. Of the variety of strain typing methods available, pulsed-field gel electrophoresis (PFGE) has proven to be more discriminating among MRSA strain types than other typing methods (e.g. multilocus sequence typing, etc.). Specifically, PFGE has been more successful at distinguishing between clusters of strains with different virulence characteristics and different epidemiological profiles [14]. Consequently, the results from this method of strain typing are an important component in identifying an MRSA infection as healthcare-associated (HA) or community-associated (CA).

The U.S. Centers for Disease Control and Prevention (CDC) used PFGE to characterize a large number of domestically occurring MRSA isolates and establish a

national database of PFGE patterns in 2003. Eight lineages were identified from these isolates and were designated as pulsed-field types (PFTs) USA100 through USA800 [14]. When epidemiologic data were linked to the isolates, it was determined that USA100 and USA200 were the two most common healthcare-associated PFTs. Less common healthcare-associated PFTs include 500, 600, and 800. These isolates had in common that they occurred in healthcare facilities, were multi-resistant to commonly used therapeutic agents, and carried the staphylococcal chromosomal cassette *mec* (SCC*mec*) type II. In contrast, USA300 and USA400 were the two community-associated PFTs. These isolates were different in that they occurred in community settings, were predominantly found in skin infections, were resistant only to β-lactam drugs and often to erythromycin, carried SCC*mec* type IV, and often harbored the Panton-Valentine leukocidin (PVL) virulence determinant. USA700 isolates were associated with both healthcare and community settings [14].

The PFGE method of MRSA strain typing has been adopted nationally based on validation studies and its accuracy, which provides researchers with a consistent and standardized tool to differentiate between HA-MRSA and CA-MRSA isolates. There are still problems, however, that remain with PFGE typing. It requires three days to perform, is expensive, calls for specialized laboratory training, is not readily available in most clinical laboratories, and lacks any patient details. Therefore, the challenge remains to find a faster, less expensive, and more readily available way to identify MRSA infections as healthcare- versus community-associated, while matching the discriminatory ability of PFGE profiles and considering patient characteristics. A more efficient and less expensive method of discrimination between HA- and CA-MRSA infections could allow

for more prompt and effective transmission prevention and timely risk intervention efforts.

This investigation uses a subset of the Michigan MRSA surveillance dataset, which was previously analyzed to address the potential for misclassifying MRSA infections as healthcare- or community-associated when using only a single classification scheme; healthcare risk factor, infection type, or susceptibility pattern. This subset comprises 244 MRSA cases with both classification data and PFGE typing results available. Logistic regression was used with PFGE result as the outcome variable and potential predictors including gender, race, age, hospitalized, survival, preexisting medical conditions, healthcare risk factor, infection type, and susceptibility pattern. Sensitivity, specificity, and predictive values were calculated, and receiver operating characteristic (ROC) curves were plotted. Discriminant analysis was used to confirm results. The goal of this research was to improve prediction of MRSA infections as healthcare- or community-associated, as determined by PFGE test result, by using multivariable statistical methods, in contrast to previous methods that have based categorization on a single classification scheme.

Methods

Data Source

The data used for this investigation is a subset of cases collected by the Michigan Department of Community Health (MDCH) MRSA Surveillance project. MRSA surveillance was conducted by MDCH from October 1, 2004 through December 31, 2005. Surveillance was carried out as a designated medical research project for public

health purposes, which permits collection of data of public health significance without having to revise the reportable disease list to make this reporting mandatory. This allows for more specific data from both HA-MRSA and CA-MRSA infections to be collected to help epidemiologically characterize these cases in Michigan. The data submission for individual MRSA cases under this designation is voluntary, although the reporting of MRSA *outbreaks* is mandatory by law in Michigan. This research project was approved by the MDCH Chief Medical Executive and the MDCH Human Subjects Committee, as well as the University of Michigan Institutional Review Board. The request to report individual MRSA cases to MDCH was announced statewide via letters, updates to reporting guidelines, and presentations to healthcare providers, laboratories, and local health departments throughout the state. Individual cases of MRSA infection were voluntarily reported through local health departments to the MDCH Antimicrobial Resistance Epidemiologist. Information was submitted using a two-page MDCH MRSA Surveillance Case Report Form and laboratory susceptibility test result sheets.

From the 2,151 total cases available, molecular typing using PFGE was conducted on 244 of these [14, 15]. A subset of the isolates was tested due to the cost and time associated with PFGE testing. The tested isolates were randomly selected from a compiled list of cases that had both sufficient epidemiologic data provided on the submitted case report form and an isolate submitted for PFGE testing. These 244 MRSA cases were used in the current analyses.

Data Management

PFT results from the PFGE molecular typing of the 244 MRSA infection isolates were used to categorize the cases as either healthcare- or community-associated [14].

Cases identified as USA100, USA200, USA600, or USA800, were defined as HA-MRSA. Cases identified as USA300 or USA400 were defined as CA-MRSA. PFTs USA500 and USA700 were not represented in the 244 PFGE results.

The 244 cases were additionally categorized as HA-MRSA or CA-MRSA by the three commonly used classification schemes: healthcare risk factor, infection type, and susceptibility pattern. Cases were labeled as HA-MRSA on the basis of healthcare risk factor if they had at least one of the following established risk factors: were hospitalized >48 hours prior to the current infection (i.e., patient was not MRSA-infected at time of hospitalization but culture and infection were identified > 48 hours after admission), were in an intensive care unit (ICU) >48 hours prior to the current infection, were hospitalized in the previous year (i.e., admitted and discharged from a hospital at any time during the year prior to the current infection), had surgery in the previous year, received dialysis in the previous year, had a percutaneous device or indwelling catheter in the previous year, or if they resided in a long-term care (LTC), nursing home or rehabilitation facility in the previous year [16-18]. Cases with "no" reported for all seven HA-MRSA risk factors (i.e., had none of the established risk factors) were considered CA-MRSA by default.

Cases were labeled as CA-MRSA on the basis of infection type if a skin or soft tissue infection was diagnosed, including abscess, cellulitis, folliculitis, and impetigo, or if a wound infection had "skin" identified as the culture site. Cases with other and more serious infections, including bacteremia, meningitis, osteomyelitis, pneumonia, septic arthritis, and surgical site infection were labeled as HA-MRSA. CA-MRSA can, in some situations, cause more serious infections like pneumonia or bacteremia, but these infections are more typically caused by HA-MRSA and are usually accompanied by the

HA-MRSA risk factors previously listed [8, 19]. Therefore, if a case had both a skin or soft tissue infection and more invasive infection concurrently, it was considered HA-MRSA to give more weight to the more serious infection type. Only thirteen cases met this criterion with either skin/soft tissue infection and bacteremia (n=8) or skin/soft tissue infection and pneumonia (n=5) present simultaneously.

Cases were labeled as CA-MRSA on the basis of susceptibility pattern if their isolates were resistant only to β-lactams, including cephalosporins and carbapenems. This is the basic resistance pattern that defines MRSA [20]. Cases were labeled as HA-MRSA if resistance to additional antimicrobial classes beyond β-lactams, including cephalosporins and carbapenems, was also reported. This higher resistance included, but was not limited to, aminoglycosides, folate pathway inhibitors, lincosamides, fluoroquinolones, and tetracyclines. Erythromycin, a macrolide, was not used in the susceptibility pattern categorization, based on research showing increased CA-MRSA resistance to erythromycin [11, 14, 21] and the large overall proportion of erythromycin-resistance in this Michigan dataset.

The three defined categorization schemes: healthcare risk factor, infection type, and susceptibility pattern, are treated as three separate dichotomous classification variables (HA=1/CA=0) in all of the analyses described for this investigation. The other predictor variables considered for this investigation were gender, race, age, hospitalized during time of MRSA infection (yes/no), survival during time of MRSA infection (died/survived), and any preexisting medical conditions (yes if reported any – diabetes mellitus, chronic renal insufficiency, dialysis, cardiovascular disease, coronary heart failure, chronic obstructive pulmonary disease/no – if none reported).

Data Analysis

Univariate analyses were conducted to compare the demographic and clinical patterns of HA-MRSA versus CA-MRSA infections when classified by PFGE result. Frequencies, percentages, and distributions of HA-MRSA and CA-MRSA infections are reported by gender, race, age, hospitalized during time of MRSA infection, survival during time of MRSA infection, preexisting medical conditions, healthcare risk factors, infection type, and susceptibilities to specific antimicrobial agents. Chi-square and Fisher's exact tests (when expected cell frequencies were <5) were performed on categorical variables to test for significant differences in proportions between HA-MRSA and CA-MRSA cases. The t-test was used to make the comparison between HA-MRSA and CA-MRSA cases for the continuous age variable.

Single-variable logistic regression models with PFGE HA vs. CA categorization as the outcome were used to test the significance of the HA/CA categorizations of each of the three classification variables: healthcare risk factor, infection type, and susceptibility pattern, as well as the demographic and other clinical variables: gender, race, age, hospitalized during time of MRSA infection (yes/no), survival during time of MRSA infection (died/survived), and any preexisting medical conditions (yes/no). For the three dichotomous classification variables, sensitivity, specificity, predictive values and McNemar's test statistics with exact p-values were calculated.

Multivariable logistic regression analyses were conducted, testing demographic and clinical variables along with the three dichotomous (HA=1/CA=0) classification variables using the method of best subset selection. Combinations of these variables were examined to identify models with the best fit and predictive power.

For the best model, the results were used to plot an ROC curve. An optimal cutpoint from the ROC curve was identified, based on maximizing the sensitivity and specificity and minimizing the discordance between the PFGE result and predicted result. This point then served as the cutpoint for the new predicted categorization of MRSA as HA or CA. Predicted probabilities of HA were computed for each of the 244 cases [Predicted Probability = $\exp(X\beta) / 1+\exp(X\beta)$]. If the predicted probability for a case was equal to or greater than the cutpoint value, it was classified as HA-MRSA, and if it was less than the cutpoint, it was classified as CA-MRSA.

Discriminant analysis was also conducted using the same predictive variables as those used for the logistic regression analyses, to verify the best model and classification results. Comparisons were made to show similarities between results from the logistic regression analyses and the discriminant analysis. All results were considered statistically significant if the p-value was <0.05. All statistical analyses were conducted using SAS® statistical software (SAS System for Windows V9.1.3, SAS Institute Inc., Cary, NC).

Results

The study dataset consisted of 244 cases of which 130 (53%) were male. The race/ethnicity distribution was as follows: 151 (62%) white, 39 (16%) black, 10 (4%) "other" (which included Hispanic/Latino, American Indian/Alaskan Native, Asian, and Native Hawaiian/Pacific Islander), and 44 (18%) unknown. The mean age was 52 years old (s.d.=25 years). In this population, 176 (72%) were hospitalized during time of MRSA infection, 21 (9%) died during time of MRSA infection, 205 (84%) had at least

one preexisting illness reported, while 21 (9%) were reported as having no preexisting illnesses and 18 (7%) were reported as unknown for preexisting illness. These distributions for gender, race, and age are similar to those of the total dataset of 2,151 MRSA cases. The proportions that were hospitalized ($p<0.0001$), died ($p=0.005$), and had at least one preexisting illness ($p<0.0001$) were significantly higher for the subset compared to the total dataset (n=2,151 – comparative data not shown).

There were 159 (65%) cases defined as HA-MRSA and 85 (35%) defined as CA-MRSA when the 244 MRSA cases in the study dataset were categorized by PFGE result (Table 3.1). There were slightly more males with MRSA infections compared to females, but the distributions between the HA- and CA-MRSA categories were not significantly different ($p=0.6445$) for gender. The higher proportion of whites was in the HA-MRSA group, but the higher proportion of blacks was in the CA-MRSA group ($p=0.0083$). The mean age for HA-MRSA infections was 60 years old (s.d.=22 years), and for CA-MRSA was 36 years old (s.d.=21 years) ($p<0.0001$). The highest proportions of HA-MRSA infections occurred among those 50 years and older, while the highest proportions of CA-MRSA infections occurred among those younger than 50 years old ($p<0.0001$) (Figure 3.1). Eighty-eight percent of the individuals with HA-MRSA infections were hospitalized during time of MRSA infection, while 49% with CA-MRSA were hospitalized ($p<0.0001$). Of the individuals with HA-MRSA, 12% died during time of MRSA infection compared to 4% with CA-MRSA ($p<0.0506$). HA-MRSA infected individuals suffered from more preexisting illnesses than those with CA-MRSA, including diabetes mellitus ($p=0.0012$), chronic renal insufficiency ($p=0.0175$), cardiovascular disease ($p=0.0002$), coronary heart failure ($p=0.0047$), chronic obstructive

pulmonary disease (p=0.0002), and overall "any" preexisting illnesses (p=0.0054). Those with HA-MRSA infections were more likely to have: been hospitalized >48 hours prior to the current infection (p<0.0001), in ICU >48 hours prior to the current infection (p=0.0057), hospitalized in the previous year (p=0.0002), had surgery in the previous year (p=0.0292), had a percutaneous device or indwelling catheter in the previous year (p<0.0001), and/or resided in a LTC, nursing home or rehabilitation facility in the previous year (p=0.0032) compared to those with CA-MRSA. Among the five most common of the infection types investigated, individuals with CA-MRSA were most likely to have skin/soft tissue infections (p<0.0001), while those with HA-MRSA had bacteremia (p=0.0010) and pneumonia (p=0.0003). The proportion of individuals with surgical site infections and/or "wound" infections did not differ significantly between the HA- and CA-MRSA groups (p=0.2462 and p=0.4677, respectively). Of the non-β-lactam drugs evaluated, the HA-MRSA infected group was more likely to be resistant to ciprofloxacin (p=0.0003), clindamycin (p<0.0001), and levofloxacin (p<0.0001) compared to the CA-MRSA group.

Results for the two-by-two comparisons between the HA-MRSA and CA-MRSA categorization based on PFGE and the categorization based on the three different classification schemes: healthcare risk factor, infection type, and susceptibility pattern are presented in Table 3.2. Sensitivities, specificities, predictive values (PV), and exact p-value results from McNemar's test for agreement for each of the three comparisons are shown. Because each of the classifications being compared in the two-by-two tables has the same two infection categories, HA-MRSA and CA-MRSA, the sensitivity for identifying a HA-MRSA infection is equal to the specificity for identifying a CA-MRSA

infection. This inverse relationship exists for all of the calculations. HA sensitivity/CA specificity (94%) and CA PV-positive/HA PV-negative (85%) are highest for the susceptibility pattern classification when all three methods are compared to PFGE result, while CA sensitivity/HA specificity (69%) and HA PV-positive/CA PV-negative (84%) are highest for the infection type classification. McNemar's tests reveal that the direction of this classification based on the infection type and healthcare risk factor will be balanced (in the same direction), while classification based on susceptibility pattern will misclassify in an unbalanced way ($p=0.0034$).

The goal of the logistic regression analyses was to use the available variables to identify a best model with a good fit and a high predictive power. This was accomplished through model building with PFGE result as the outcome, using the log-likelihood statistic and Max-rescaled R^2 statistic to assess model fit (Table 3.3). Each of the classification variables was significant when tested alone in the model (Models 1-3, for each variable $p<0.0001$), but susceptibility pattern (-2 Log L = 212.61 and Max-rescaled $R^2 = 0.460$) was better in the model than infection type (-2 Log L = 224.39 and Max-rescaled $R^2 = 0.343$), which was better then healthcare risk factor (-2 Log L = 275.90 and Max-rescaled $R^2 = 0.206$). Infection type and susceptibility pattern were the best combination, when the three classification variables were tested in pairs (Models 4-6). The healthcare risk factor classification variable, added to the model with classification variables infection type and susceptibility pattern, only slightly improved the fit and predictive power and was not significant in the model; therefore it was eliminated (Model 7). Infection type and susceptibility pattern classification variables were used as the base model, and demographic and clinical variables were then tested in

this model. These additional variables were significant individually with PFGE result as the outcome, as well as individually with each of the two base variables, and included age, hospitalized, survival, and preexisting illnesses (individual testing data not shown). Each of these variables tested separately in the base model (with infection type and susceptibility pattern) did increase the fit and predictive power of the model. Age and hospitalized were most effective at increasing the fit and predictive power of the model, while survival was not significant in the model (Models 8-11). All four of the additional variables were then tested together in the base model with infection type and susceptibility pattern to identify the maximum possible fit and predictive power levels (Model 12). The preexisting illnesses variable was removed with very little change to the fit and predictive power levels, and it did not test significant in the model (Model 13). The survival variable was removed last, with only slight decreases in the fit and predictive power, and it did not test significant in the model (Model 14). The identified final best model included the classification variables infection type and susceptibility pattern, as well as age and hospitalized, and is identical to the model identified using best subset selection. Figure 3.2 illustrates the distribution of logit probabilities for the HA-MRSA and CA-MRSA groups as defined by PFGE result from the final best model. The HA cases are more tightly clustered compared to the CA cases, which are more dispersed and have a number of cases overlapping the HA logit probabilities.

The ROC curve based on the final best logistic regression model is plotted in Figure 3.3. This plot is not symmetrical showing that the sensitivity for HA is higher than the sensitivity for CA. The optimum cutpoint corresponded to a predicted probability of HA of 0.614, with a HA sensitivity of 93.6% and a HA specificity of

80.3%. To predict whether a case of MRSA infection is healthcare-associated or community-associated, from the logistic regression and ROC curve analyses, the following equation was used:

Logit (p) = -4.095 + (1.722*Infection Type) + (2.236*Susceptibility Pattern) + (0.021*Age) + (1.379*Hospitalized)

Age is a continuous variable, Hospitalized is yes/1 or no/0, Infection Type and Susceptibility Pattern are HA/1 or CA/0 based on previously explained definitions.

If Predicted Probability >= 0.614 then Predict = HA-MRSA

If Predicted Probability < 0.614 then Predict = CA-MRSA

Examples:

1	Logit (p)= -4.095+(1.722*1)+(2.236*1) +(0.021*62)+(1.379*1)=2.54	Predicted Prob = 12.68/13.68=0.93	Predict=HA-MRSA since 0.93>0.614
2	Logit (p)= -4.095+(1.722*0)+(2.236*0) +(0.021*19)+(1.379*0)=-3.70	Predicted Prob = 0.025/1.025=0.02	Predict=CA-MRSA since 0.02<0.614

In order to test the symmetry of matching between the PFGE result and the new Predict result, these two variables were compared through McNemar's test. The results (test statistic= 0.667, p=0.54) revealed that if misclassifications occur, the two methods misclassify subjects in a balanced way, equally in both directions.

Discriminant analysis has been reported to be less preferable compared to logistic regression in situations where observations are classified on the basis of categorical variables [Press and Wilson, 1978 and SAS® Users Guide]. In spite of this caveat, this analysis was conducted and revealed similar best model and classification results as the logistic regression and ROC curve analyses. The total error rates from the discriminant analysis estimates are listed in Table 3.3 (see Chapter III Appendix for further details).

Discussion

The goal of this research was to improve classification of MRSA infections as healthcare- or community-associated using multivariable statistical methods, in contrast to the currently employed classification schemes; healthcare risk factor, infection type, or susceptibility pattern. HA- and CA-MRSA infections often present among disparate age groups and in individuals with different risk factors. They are distinct in the types of infections they cause, their transmission risk, and in the different treatment modalities they require [11, 22-25]. A more efficient method of discrimination between HA- and CA-MRSA, in the absence of PFGE results, could allow for more prompt and effective transmission prevention and risk intervention efforts.

This study dataset of 244 cases is similar by gender, race, and age to the total Michigan MRSA Surveillance dataset of 2,151 cases from which it was selected. However, the subset has more cases with hospitalizations, deaths, and preexisting illnesses relative to the total dataset. This is likely due to the greater proportion of healthcare-associated cases in the subset, because of the greater probability that healthcare facilities had cultures available for submission from reported cases. Obtaining cultures for cases reported from the community setting proved more difficult. The results from this investigation are not affected by a proportional difference between HA-MRSA and CA-MRSA, because the numbers are sufficiently high in both category types to draw distinctions and make comparisons.

MRSA infections in this study dataset of 244 cases are defined as HA or CA by PFGE result (Table 3.1). The demographic, clinical, and microbiologic variables reveal expected distributions that are consistent with those seen in previously published

literature, according to the differing presentations of these two MRSA types [10-13, 22-26]. Individuals at increased risk for acquisition of HA-MRSA are generally older, often with weaker immune systems and more preexisting illnesses. Their medical problems may require frequent visits and treatments at healthcare facilities, and they often end up with systemic, resistant infections. CA-MRSA usually affects otherwise healthy individuals with no preexisting illnesses and tends to mostly cause skin and soft tissue infections. The non-significant difference between HA and CA groups in this study dataset for surgical site infections and "wound" infections is likely due to the low numbers of surgical site infections and to the vagueness of the term "wound" infection, which is generically used to describe infections in both healthcare and community settings. The majority of both HA and CA infections were among white subjects, but among blacks the proportions of CA infections were significantly higher than HA infections. These results correspond with other studies that have shown an increased risk for CA-MRSA infections and colonization in blacks [27-29].

A number of variables were considered in the development of the new model to more accurately define MRSA infections as HA or CA, using PFGE result as the gold standard for comparison. Four variables were chosen for the final model, and three of the seven tested variables were eliminated during the analytic selection process. The classification variables infection type and susceptibility pattern were selected along with age and hospitalized for inclusion in this new model. The additional inclusion of age and hospitalized is not too surprising as the age distributions for HA- and CA-MRSA infections have been shown to be unique from one another [30-33] and hospitalization is more likely to occur among the more invasive HA-MRSA infections [8, 19]. The

existing differences between the HA and CA groups for each of these four variables, along with the high likelihood that the easily obtained data are accurate, makes them strong contributors to the new categorization model. It is likely that the preexisting illnesses variable was eliminated from the model because it is generally difficult to consistently obtain an accurate history on patients, as it is to obtain information on healthcare risk factors. As the prevalence of CA-MRSA in the community setting continues to increase, an individual with healthcare risk factors could be at greater risk for acquisition of CA-MRSA from their community than risk for acquisition of HA-MRSA from the healthcare settings with which they interact. Although healthcare risk factor wasn't included in the model, this model serves as a proxy measure for this information, and includes variables that are easier to obtain accurately. As long as the delineation exists between the common settings for HA- and CA-MRSA, this information from the new model will help identify where an infection was most likely acquired, which is pertinent knowledge for appropriately targeting infection control and transmission prevention efforts. The survival variable (died during time of MRSA infection) was also eliminated from the best model. It could represent severity of the infection, like the hospitalized variable, however only a small number of all HA-MRSA infections die and often deaths attributed to MRSA are not coded accurately [34]. Therefore, its usefulness as a contributing predictor in the model is not as strong as hospitalized. The data reported for hospitalized during time of MRSA infection and survival during time of MRSA infection serve as proxy measures within the time frame of the MRSA infection. The ability of the hospitalized variable to contribute to the model

and of the survival variable to be a contributing predictor at all may be stronger if the data collected for these variables were strictly due to MRSA.

These analyses were run to predict the probability of HA from the dichotomous PFGE outcome variable HA (1) and CA (0). The HA vs. CA outcome for these analyses made the sensitivity/specificity analysis slightly more complicated than with a disease/no disease outcome. The sensitivity for a HA-MRSA case is the specificity for a CA-MRSA case and the sensitivity for a CA-MRSA case is the specificity for a HA-MRSA. The ROC curve (Figure 3.3) shows that there is no point from this dataset that would give an equal sensitivity and specificity for both HA- and CA-MRSA infections. At the chosen optimum cutpoint, the sensitivity for defining a true HA-MRSA case is 93.6%, but the sensitivity for defining a CA-MRSA case is 80.3%. These results are explained by Figure 3.2. The plot of the logit result from the best model shows that the HA-MRSA cases are clustered tightly and only a few lie outside of this cluster. In contrast, the CA-MRSA cases are more dispersed and a larger number are scattered across the HA-MRSA values. Therefore, the ability to accurately identify a HA-MRSA case is greater than the ability to accurately identify a CA-MRSA case.

This investigation to identify a new method of MRSA categorization has some limitations. The number of cases used in this model building (n=244) was relatively small, due to a limited number of available PFGE results among the total cases reported (N=2,151). Additionally, observations with missing values were excluded from the analyses resulting in smaller sample sizes (See Table 3.3: range based on the analysis run n=204-244). Use of a larger sample size in the analyses would increase the power to identify the best variables to accurately define an MRSA infection as HA or CA. The

model equation was developed from data collected through voluntary Michigan MRSA surveillance conducted in 2005. Consequently, it would be helpful to rerun these analyses with a larger, updated Michigan dataset for validation. These data are considered to be representative of the range of residents who acquire MRSA infections in Michigan, although they may not be representative of MRSA infections in other areas. It must be determined whether the best model identified in this research is appropriate for other areas of the nation. A reasonable next step would be to repeat the presented analyses with large datasets from other states, and if possible, with a national MRSA dataset. The methods used to develop this model incorporate common and widely utilized statistical analyses, so it would be feasible to repeat the steps of model development using data from other areas. The HA- and CA-MRSA profiles are constantly changing and the settings where these infections are identified increasingly intersect [35-37]. Therefore, this cannot be a static model, but must be continually updated and revised to account for differences and changes in MRSA profiles. In spite of the limitations, the new proposed model identifies a combination of basic variables already acknowledged and widely used in differentiating HA- from CA-MRSA infections, and is likely to improve on the accuracy of categorizing MRSA infections in and outside of Michigan.

In conclusion, the analyses of this investigation have identified a new multivariable model to define MRSA infections as HA or CA. Individually the variables have all been long recognized to relate to MRSA infection, but the use of the four covariates (infection type, susceptibility pattern, age, and hospitalized) in combination in a predictive statistical model is new and should improve accuracy in the categorization of

MRSA. This model can provide a fast and accurate way for a healthcare system or health department to identify MRSA infections as HA or CA. Knowing which type of MRSA is causing infections provides greater opportunity for the most accurate and targeted educational messages to patients and caregivers for control of transmission. This is critical to successful prevention programs aimed at controlling increasing resistance and spread of MRSA.

Acknowledgements

We thank all of the Michigan public health professionals, laboratorians, infection preventionists, and health care providers who dedicated extra time and effort to collect and report these important MRSA data. We also thank David Dixon and the MDCH Houghton Laboratory for isolate collection and PFGE testing, and Steve Cali for his diligent data entry efforts.

Table 3.1. Michigan MRSA Infections Classified by PFGE Result as Healthcare-Associated (HA) or Community-Associated (CA).

Demographic/Characteristic	Healthcare-Associated	Community-Associated	*p*-value*
Total N=244	N=159 (65%) n (%)	N=85 (35%) n (%)	
Gender: Male	83 (52)	47 (55)	0.6445
Race: White	107 (82)	44 (63)	0.0083
Black	19 (15)	20 (29)	
Other	4 (3)	6 (8)	
Age 0-80+	155 ($\bar{x}$=60 s.d.=22)	82 ($\bar{x}$=36 s.d.=21)	<0.0001
Hospitalized: Yes	138 (88)	38 (49)	<0.0001
Survival: Died	18 (12)	3 (4)	0.0506
Preexisting Illness(s):			
None	9 (6)	12 (17)	0.0069
Diabetes Mellitus	65 (41)	14 (19)	0.0012
Chronic Renal Insufficiency	30 (19)	5 (7)	0.0175
Cardiovascular Disease	46 (29)	5 (7)	0.0002
Coronary Heart Failure	38 (24)	6 (8)	0.0047
COPD	48 (31)	6 (8)	0.0002
Any Underlying Illness	148 (94)	57 (83)	0.0054
Healthcare Risk Factors:			
Hospitalized >48 hours	44 (28)	2 (2)	<0.0001
In ICU >48 hours	21 (13)	2 (2)	0.0057
Hospitalized in Prior Year	96 (60)	30 (35)	0.0002
Surgery in Prior Year	55 (35)	18 (21)	0.0292
Indwell Device in Prior Yr	55 (35)	8 (9)	<0.0001
LTC/Rehab in Prior Year	40 (25)	8 (9)	0.0032
Infection Type:			
Bacteremia	23 (16)	1 (1)	0.0010
Pneumonia	42 (29)	6 (8)	0.0003
Skin / Soft Tissue	23 (16)	53 (69)	<0.0001
Drug Resistance:			
Ciprofloxacin	20 (95)	4 (33)	0.0003
Clindamycin	99 (83)	8 (14)	<0.0001
Levofloxacin	142 (93)	23 (28)	<0.0001

* *p*-values shown are from χ^2 tests for categorical variables, Fisher's exact test for Ciprofloxacin and t-test for Age.

Figure 3.1. Age Group Distribution for Michigan MRSA Infections Classified by PFGE Result as Healthcare-Associated (HA) or Community-Associated (CA).

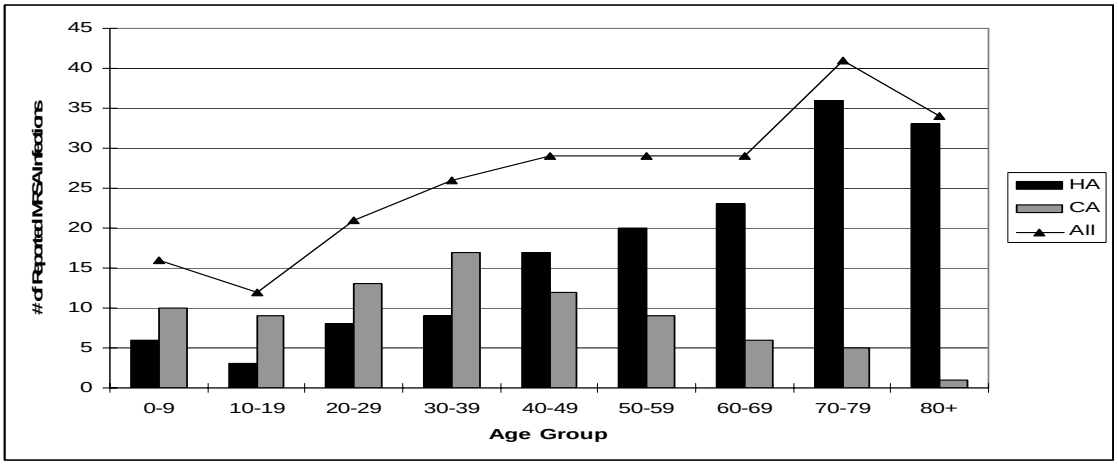


Table 3.2. Comparisons of PFGE Results by Healthcare Risk Factor, Infection Type, and Susceptibility Pattern for Michigan MRSA Infections Classified as Healthcare-Associated (HA) or Community-Associated (CA).

PFGE Results By:	HA-Sensitivity CA-Specificity	CA-Sensitivity HA-Specificity	HA-Predictive Val.+ CA-Predictive Val.-	CA-Predictive Val.+ HA-Predictive Val.-	McNemar's Test Exact *p*-value
Healthcare Risk Factor	81%	59%	79%	63%	0.6201
Infection Type	84%	**69%**	**84%**	70%	1.0000
Susceptibility Pattern	**94%**	65%	83%	**85%**	0.0034

Table 3.3. Logistic Regression Results with PFGE Result as Outcome Variable for Michigan MRSA Infections Classified as Healthcare-Associated (HA) or Community-Associated (CA).

MODEL	Healthcare Risk Factors *p*-value	Infection Type *p*-value	Susceptibility Pattern *p*-value	Age *p*-value	Hospitalized *p*-value	Survival *p*-value	Preexisting Illnesses *p*-value	-2 Log-likelihood	Max-rescaled R^2	Total Error Rate-Discrim Estimate
1 (n=244)	<.0001	---	---	---	---	---	---	275.90	0.206	0.3002
2 (n=224)	---	<.0001	---	---	---	---	---	224.39	0.343	0.2341
3 (n=239)	---	---	<.0001	---	---	---	---	212.61	0.460	0.2049
4 (n=224)	0.0004	<.0001	---	---	---	---	---	211.94	0.399	0.2263
5 (n=239)	0.008	---	<.0001	---	---	---	---	205.86	0.486	0.2049
6 (n=221)	---	<.0001	<.0001	---	---	---	---	176.90	0.532	0.1721
7 (n=221)	0.189	<.0001	<.0001	---	---	---	---	175.23	0.539	0.1721
8 (n=215)	---	<.0001	<.0001	0.012	---	---	---	158.65	0.581	0.1311
9 (n=217)	---	<.0001	<.0001	---	0.0005	---	---	163.09	0.571	0.1601
10 (n=213)	---	<.0001	<.0001	---	---	0.372	---	167.52	0.543	0.1646
11 (n=221)	---	<.0001	<.0001	---	---	---	0.040	172.79	0.548	0.1604
12 (n=204)	---	<.0001	<.0001	0.129	0.005	0.206	0.433	138.81	0.625	0.1277
13 (n=204)	---	<.0001	<.0001	0.040	0.002	0.229	---	139.42	0.622	0.1275
14 (n=211)	**---**	**<.0001**	**<.0001**	**0.024**	**0.004**	**---**	**---**	**147.93**	**0.607**	**0.1448**

Note: See text for variable definitions. The Wald Global χ^2 *p*-values for all logistic regression models above (1-14) were <0.0001.

Figure 3.2. PFGE result predicting the probability of HA (vs. CA) infection by logistic regression with predictors including infection type, susceptibility pattern, age, and hospitalized.

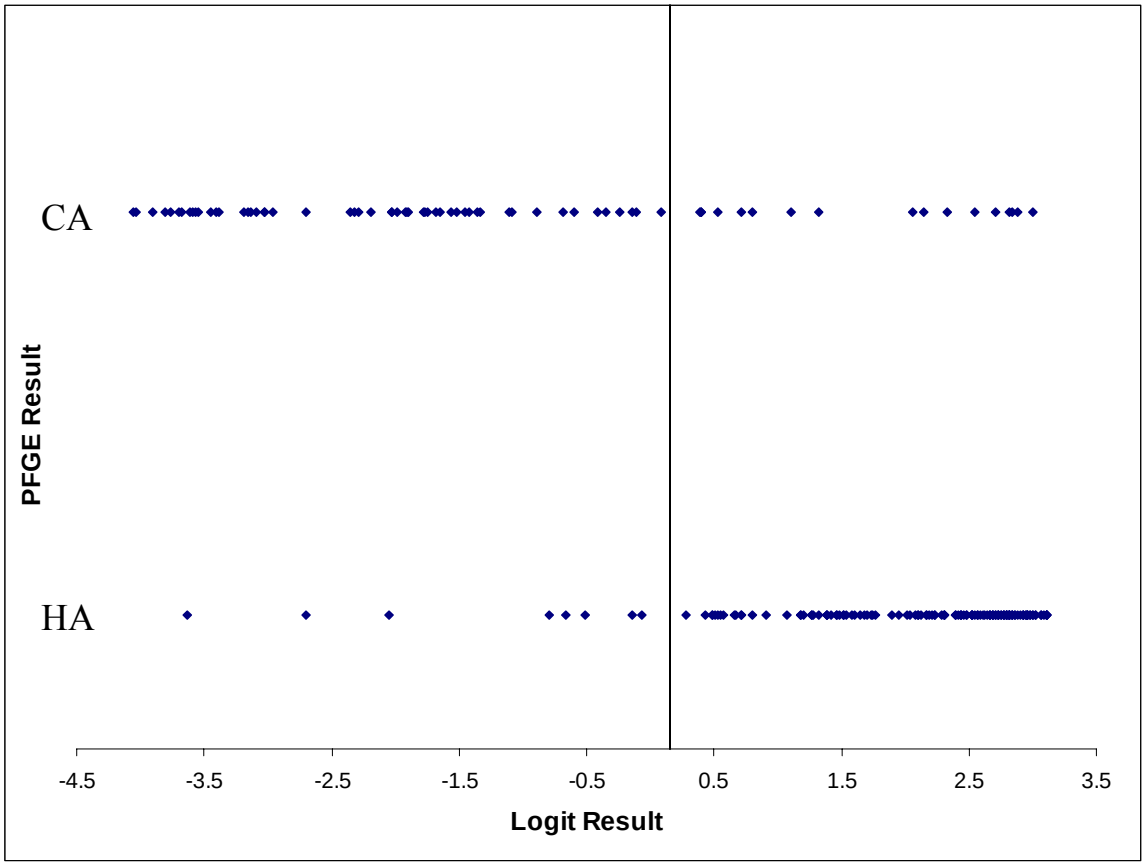
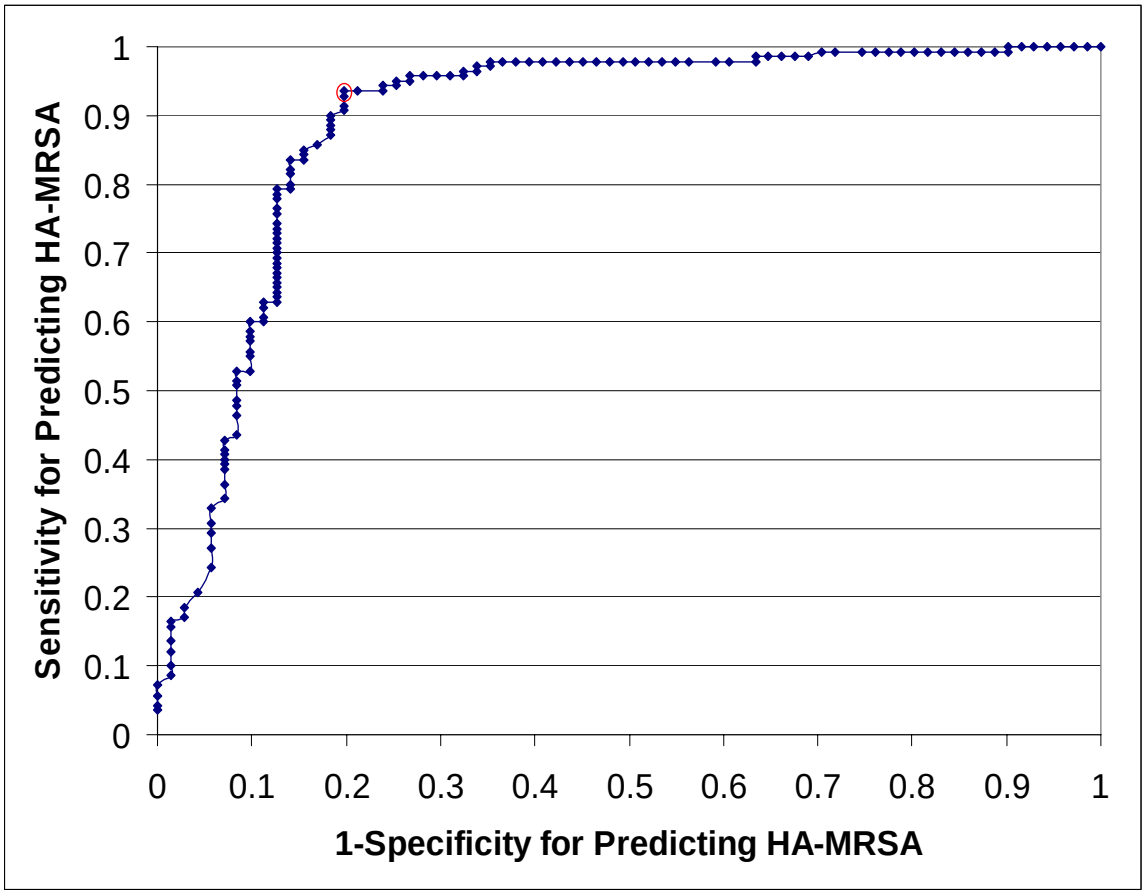


Figure 3.3. ROC curve output from best logistic model identified to predict the dependent variable PFGE result=HA. This model included infection type, susceptibility pattern, age, and hospitalized.



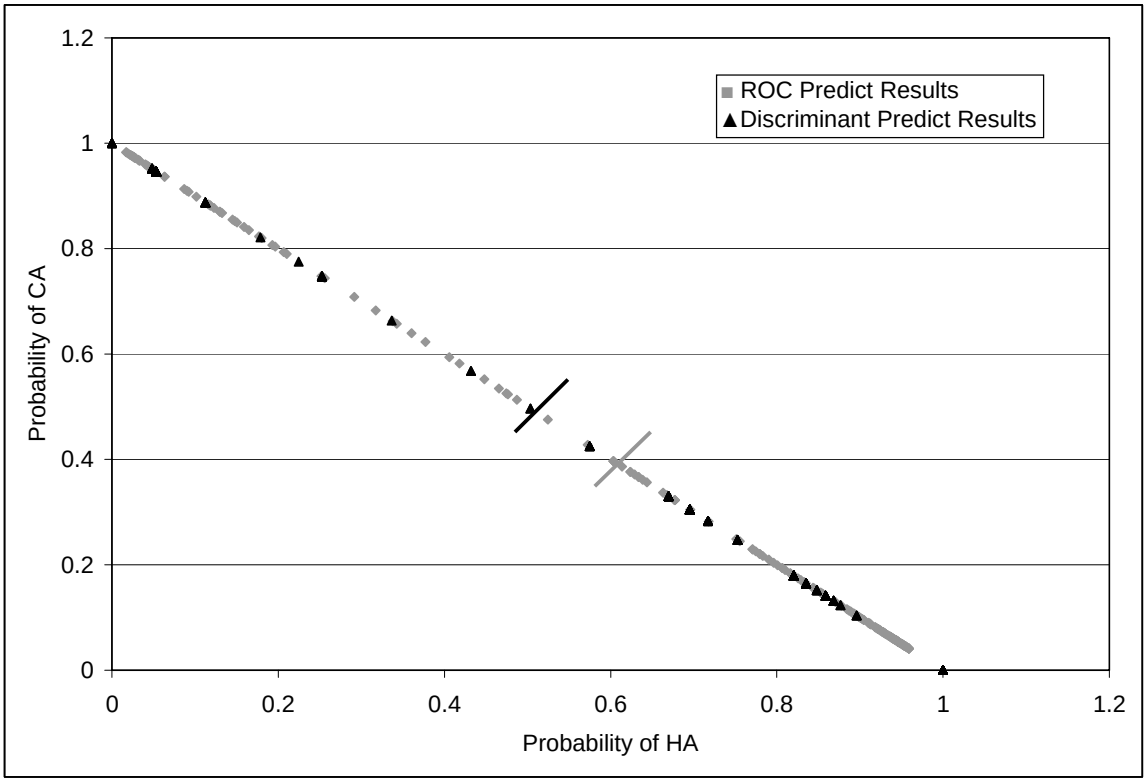
Circle Shown above is at sensitivity point=0.936 and 1-specificity point=0.197.

Appendix

The goal of the discriminant analysis was to minimize the error rate. Procedures run in the discriminant analysis using the same variables that were tested in the logistic regression models revealed very similar results. Susceptibility pattern alone decreased the error rate by a greater amount than infection type, which was better then healthcare risk factor (Models 1-3). The three classification variables were tested in pairs, and infection type and susceptibility pattern were the best combination (Models 4-6). Healthcare risk factor variable was added to the model with infection type and susceptibility pattern with no change in the error rate, therefore it was not necessary in the model (Model 7). Age, hospitalized, survival, and preexisting illnesses were tested in the model alone with infection type and susceptibility pattern. Each of these variables did decrease the error rate, though age and hospitalized were most effective, and survival was least effective (Models 8-11). All four of the additional variables were tested together in the base model with infection type and susceptibility pattern and the error rate did decrease a good deal (Model 12). The preexisting illnesses variable was removed with very little change in the error rate (Model 13). The survival variable was removed with only a small increase in the error rate noted (Model 14). Discriminant analysis, therefore, showed similar findings and best model identification as reported from logistic regression analysis. Discriminant analysis was run to predict whether a case was HA-MRSA or CA-MRSA using the data from the 244 cases in the best model and results were very similar to the ROC curve analysis. The cutpoint identified from the data output in the discriminant analysis matched to a ROC probability point of 0.603, which was very close to the optimal probability point of 0.614 that was identified in the ROC

curve analysis. When the predict results from the ROC curve analysis were plotted against the discriminant analysis results, only four cases were discordantly identified as a HA- or CA-MRSA infection out of the 211 analyzed with no missing variables (Appendix Figure 3.1). In order to verify an accurate match between the PFGE result and the discriminant result, these two variables were compared through McNemar's test. The results (test statistic=1.96, p=0.23) showed that if misclassification occurs, the two methods misclassify in a similar way.

Appendix Figure 3.1. Probability of healthcare-associated (HA) categorization versus probability of community-associated (CA) categorization for ROC Predict results and Discriminant Predict results.



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Chapter IV

Profile of Healthcare- and Community-Associated Methicillin-Resistant *Staphylococcus aureus* Infections in Michigan Using a New Multivariable Classification Model

Abstract

Background: A variety of classification schemes have been used to define methicillin-resistant *Staphylococcus aureus* (MRSA) infections as either healthcare-associated (HA) or community-associated (CA). Three of the most common methods (healthcare risk factor, infection type, susceptibility pattern) have been shown to produce discordant results when compared. We have previously developed a new classification model (Chapter III) to more accurately define MRSA as HA or CA, which closely approximates pulsed-field gel electrophoresis (PFGE) categorization. The variables included in this new model are infection type, susceptibility pattern, age, and hospitalization during the time of infection. This current investigation demonstrates the improved accuracy of the multivariable classification model and uses the new model to better define the epidemiology of MRSA infections in Michigan.

Methods: MRSA infections were voluntarily reported in Michigan to the Michigan Department of Community Health (MDCH) between October 1, 2004 and December 31, 2005. Data on patient demographics, risk factors, and infection information were recorded on the MDCH MRSA Surveillance Case Report Form and submitted to MDCH along with laboratory susceptibility test results. MRSA infections

were classified as HA or CA using PFGE test result when available, or alternatively using the new model that was identified to accurately predict MRSA type, in the absence of PFGE result. A total of 1,644 cases were included in these analyses.

Results: MRSA infections were more accurately defined as HA or CA using the new multivariable model compared to classification by healthcare risk factor alone. The results help to clarify the existing differences in risk factors, infection types, outcomes, and resistance patterns between HA- and CA-MRSA in Michigan and highlight the risk groups and facility types most in need of targeted MRSA control and prevention efforts. The greatest proportion of MRSA reports were submitted from hospital and correctional facilities. The CA-MRSA group had higher proportions of males and blacks compared to the HA-MRSA group. These data also show that MRSA is prevalent throughout Michigan and in a variety of geographic regions. The approximate MRSA prevalence estimates calculated for three Michigan healthcare systems and their surrounding catchment areas ranged from 94-196/100,000 persons.

Conclusion: The MRSA surveillance data collected has made possible this first report on HA- and CA-MRSA infections from throughout Michigan. The results, obtained using a new multivariable model to classify MRSA infections as HA or CA, provide a practical picture of the overall epidemiology of MRSA in Michigan. This information can be used to initiate more accurately targeted control efforts and educational prevention messages, in order to effectively combat this adept organism. The Michigan MRSA profile will continue to evolve, and so it is crucial that efforts to track and characterize these organisms continue.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have been categorized in a number of different ways based on various epidemiologic, clinical, and molecular criteria. One widely used classification differentiates between healthcare-associated (HA) and community-associated (CA) infections. MRSA occurring in healthcare settings or in individuals who received recent or continuous care in such a setting is referred to as healthcare-associated MRSA (HA-MRSA). MRSA identified among individuals outside of a healthcare venue and/or who have not received recent care in that setting is referred to as community-associated MRSA (CA-MRSA). HA-MRSA has been endemic in large urban medical centers in the U.S. since the 1990s [1-5] and CA-MRSA has greatly increased in prevalence since the late 1990s [6-15]. These two types of MRSA have emerged as distinct organisms with differing epidemiologic profiles in terms of risk factors, infection type presentations, and susceptibility patterns [16-26]. It is important to be able to accurately differentiate between these two types of MRSA infection, in order to treat people with proper antimicrobial therapy, respond with appropriate infection control precautions, and use the correct transmission prevention guidelines.

Pulsed-field gel electrophoresis (PFGE) testing can be considered a gold standard for distinguishing between HA- and CA-MRSA infections [27]. This molecular strain typing requires at least three days to perform, is expensive, calls for specialized laboratory training, is not readily available in most clinical laboratories, and doesn't consider patient details. Classifying HA- vs. CA-MRSA based on healthcare risk factor, infection type, or susceptibility pattern is much less resource intensive, and any or all of

these methods are regularly used by healthcare providers and researchers. However, these three criteria for differentiating HA and CA have been shown to produce discordant results when compared, making their use problematic [16, 17, 20, 22-26].

MRSA has been studied extensively. Approximately 6,730 related articles appeared on a PubMed MRSA search. Many of these articles include information on the differences between HA-MRSA and CA-MRSA infections. Most such research is derived from planned research projects, reports on outbreak investigations, or based on surveillance at sentinel sites. Currently, limited population-based data, collected and reported through systematic public health surveillance for MRSA infections are available. The reasons include limited availability of funding, the difficulty in tracking and reporting large numbers of HA-MRSA in hospitals, and challenges in identifying CA-MRSA from community settings. Consequently, most of the population-based data on HA- and CA-MRSA infections are reported from nine U.S. states (CA, CO, CT, GA, MD, MN, NY, OR, TN) that participate in the Active Bacterial Core Surveillance (ABCs) in the Emerging Infections Program through the Centers for Disease Control and Prevention (CDC) [28-35]. These sites received considerable funding allowing them to conduct surveillance (including for MRSA) that most other state health departments and healthcare facilities could not handle due to lack of resources, staff and money. Laboratory reports of positive MRSA cultures from normally sterile body sites are actively identified and epidemiologic patient data are collected and reported from the residents of defined catchment areas from each of these program sites. This surveillance has revealed that prevalence and incidence rates, groups at highest risk for acquisition, infection presentations, and molecular make-up may vary for HA- vs. CA-MRSA

organisms depending on the geographic area of the nation. Michigan is not part of this funded surveillance program and statewide characterization data do not currently exist, despite a significant impact from HA- and CA-MRSA in this region. This has been noted from the frequently large number of reported MRSA outbreaks and inquiry calls to the Michigan Department of Community Health (personal communication).

Effective control and prevention of both HA- and CA-MRSA infections in Michigan require a thorough epidemiological characterization of the problem. It is critical to clarify and understand the Michigan MRSA profile by gender, race, age, preexisting medical conditions, healthcare risk factors, types of infections, and susceptibility profiles. With this information, Michigan healthcare providers and public health professionals can be more adequately informed to appropriately implement effective infection control procedures within facilities and communities and accurately educate patients and residents in order to interrupt and prevent further transmission of MRSA.

The purpose of this investigation was to better define the epidemiology of MRSA infections in Michigan and expand upon the current population-based profile of MRSA presented in other regions of the nation. Michigan's MRSA infections are classified as HA or CA using a PFGE test when available, or alternatively using a new less resource intensive model that we developed to classify MRSA type as HA or CA, in the absence of PFGE results. The epidemiology of these Michigan HA- and CA-MRSA infections are then presented and compared. We compared categorization of HA and CA using PFGE result or results generated from the multivariable model to classification based on healthcare risk factor, to identify any existing discordance between the classification

methods and to define the groups that were classified inconsistently. Data from three healthcare systems of Michigan were used to estimate and compare MRSA prevalence in those catchment areas.

Methods

Data Source

MRSA surveillance was conducted by the Michigan Department of Community Health (MDCH) from October 1, 2004 through December 31, 2005. Surveillance was carried out as a designated medical research project for public health purposes, which permits collection of data of public health significance without having to revise the reportable disease list to make this reporting mandatory. Thus more specific data from both HA-MRSA and CA-MRSA infections were collected by public health authority. Data submission for individual MRSA cases under this designation was voluntary, although the reporting of MRSA *outbreaks* is legally required in Michigan. The medical research designation protects the submitted data and the submitter under the Public Health Code (MCL 333.2631-2635), so that confidentiality and appropriate use are guaranteed. Hence, the data are protected and inadmissible as evidence in a court, and the submitter is protected from liability for furnishing the data. This research project was approved by the MDCH Chief Medical Executive and the MDCH Human Subjects Committee, as well as the University of Michigan Institutional Review Board. The request to report individual MRSA cases to MDCH was announced statewide via letters, updates to reporting guidelines, and presentations to healthcare providers, laboratories and local health departments throughout the state. Individual cases of MRSA infection

were voluntarily reported through local health departments to the MDCH Antimicrobial Resistance Epidemiologist. Information was submitted using a two-page MDCH MRSA Surveillance Case Report Form and laboratory susceptibility test result sheets.

A total of 2,227 unduplicated MRSA cases were reported to the MDCH by correctional facilities, private physicians, infection preventionists, hospital laboratories, and local health departments throughout Michigan from October 1, 2004 through December 31, 2005. Seventy-six cases (3.4%) were excluded due to: non-MI residence (n=19), infection type specified as none (n=54) or colonization (n=3). This left 2,151 unique cases in the total Michigan MRSA infection surveillance dataset. An additional 507 (23.6%) of MRSA cases had data missing for the variables required in the new classification model and were deleted during the analyses. Therefore, 1,644 Michigan MRSA infections were analyzed in this study.

Data Management

The CDC used PFGE to characterize a large number of domestically occurring MRSA isolates and establish a national database of PFGE patterns in 2003. Eight lineages were originally identified from these isolates and were designated as pulsed-field types (PFT) USA100 through USA800 [27, 36]. PFT information through PFGE testing was available on a random selection of 244 of the 1,644 cases in the study dataset (see Chapter III). This subset of 244 cases was previously used in the analyses to develop a new statistical model to more accurately classify an MRSA infection as HA or CA. The PFT results from the 244 MRSA infection isolates were used to categorize cases as either HA or CA according to the definitions of the PFT established by the CDC [27]. Cases identified as USA100, USA200, USA600, or USA800 were defined as HA-MRSA.

Cases identified as USA300 or USA400 were defined as CA-MRSA. PFTs USA500 and USA700 were not represented in the 244 PFGE results.

The 1,400 cases without a PFGE result in the study dataset were categorized as HA- or CA-MRSA using the newly developed multivariable model to classify MRSA type. This model collectively incorporates the following variables: infection type, susceptibility pattern, age, and hospitalized as a basis for MRSA classification. Infection type and susceptibility pattern were defined for each of the 1,400 reported MRSA cases. Cases were labeled as CA-MRSA on the basis of infection type if a skin or soft tissue infection was diagnosed, including abscess, cellulitis, folliculitis, and impetigo, or if a wound infection had "skin" identified as the culture site. Cases with other and more serious infections, including bacteremia, meningitis, osteomyelitis, pneumonia, septic arthritis, and surgical site infection were labeled as HA-MRSA. CA-MRSA may in some situations cause more serious infections like pneumonia or bacteremia, but these infections are more typically caused by HA-MRSA and are usually accompanied by the HA-MRSA risk factors previously listed [18, 31]. Therefore, if a case had both a skin or soft tissue infection and more invasive infection concurrently, it was considered HA-MRSA to give more weight to the more serious infection type. Only 13 cases met this criterion with either skin/soft tissue infection and bacteremia (n=8) or skin/soft tissue infection and pneumonia (n=5) present simultaneously.

Cases were labeled as CA-MRSA on the basis of susceptibility pattern if their isolates were resistant only to β-lactams, including cephalosporins and carbapenems. This is the basic resistance pattern that defines MRSA [37]. Cases were labeled as HA-MRSA if resistance to additional antimicrobial classes beyond β-lactams, including

cephalosporins and carbapenems, were also reported. This higher level resistance included, but was not limited to, aminoglycosides, folate pathway inhibitors, lincosamides, fluoroquinolones, and tetracyclines. Erythromycin, a macrolide, was not used in the susceptibility pattern categorization, based on research showing increased CA-MRSA resistance to erythromycin [23, 27, 38] and the large overall proportion of erythromycin-resistance in the Michigan dataset.

Data Analysis

The study dataset of 1,644 MRSA infections was categorized as HA(1) or CA(0) by either PFGE result (n=244 cases) or Predict result (n=1,400 cases). A Predict result was generated for the 1,400 cases by classifying cases using the new multivariable model developed in a previous investigation of the Michigan MRSA dataset.

The model equation is:

Logit (p) = -4.095 + (1.722*Infection Type) + (2.236*Susceptibility Pattern) + (0.021*Age) + (1.379*Hospitalized)

Age is a continuous variable, Hospitalized is yes/1 or no/0, Infection Type and Susceptibility Pattern are HA/1 or CA/0 based on previously explained definitions.

Predicted Probability = [exp(Xβ) / 1+exp(Xβ)]

If Predicted Probability >= 0.614 then Predict = HA-MRSA

If Predicted Probability < 0.614 then Predict = CA-MRSA

Univariate analyses were conducted to provide a comparison of the demographic and clinical patterns of HA-MRSA versus CA-MRSA infections when classified by either PFGE or Predict result. Frequencies, percentages, and distributions of HA-MRSA and CA-MRSA infections are reported by gender, race, age, county of residence, reporting facility type, hospitalized during time of MRSA infection, survival during time

of MRSA infection, preexisting medical conditions, healthcare risk factors, infection type, and susceptibilities to specific antimicrobial agents. Chi-square and Fisher's exact tests (when expected cell frequencies were <5) were performed on categorical variables to test for significant differences in proportions between HA-MRSA and CA-MRSA defined cases. The t-test was used to make the comparison between HA-MRSA and CA-MRSA cases for the continuous age variable.

The 1,644 cases in the study dataset were also categorized as HA- or CA-MRSA by the healthcare risk factor classification scheme. Cases were labeled as HA-MRSA on the basis of healthcare risk factor if they had at least one of the following established risk factors: were hospitalized >48 hours prior to the current infection (i.e., patient was not MRSA-infected at time of hospitalization but culture and infection were identified > 48 hours after admission), were in an intensive care unit (ICU) >48 hours prior to the current infection, were hospitalized in the previous year (i.e., admitted and discharged from a hospital at any time during the year prior to the current infection), had surgery in the previous year, received dialysis in the previous year, had a percutaneous device or indwelling catheter in the previous year, or if they resided in a long-term care (LTC), nursing home or rehabilitation facility in the previous year [29, 39, 40]. Cases with "no" reported for all seven HA-MRSA risk factors (i.e., had none of the established risk factors) were considered CA-MRSA by default.

The HA and CA outcomes from categorization of the study dataset by healthcare risk factor were compared to the classification according to PFGE or Predict result to identify discordant classification. Univariate analyses were conducted to provide a comparison of the demographic and clinical patterns of HA-MRSA versus CA-MRSA

infections when classified by healthcare risk factor as done with Predict and PFGE results. The frequencies, percentages, and distributions of healthcare risk factor defined HA-MRSA and CA-MRSA infections as reported by gender, race, age, hospitalized during time of MRSA infection, survival during time of MRSA infection, preexisting medical conditions, infection type, and susceptibilities to specific antimicrobial agents were compared to results when the same 1,644 cases were classified as HA or CA by Predict or PFGE result.

MRSA prevalence estimates were calculated for three zip code-delimited areas of Michigan, representing healthcare system catchment areas. MRSA infections were consistently reported during the entire period of the surveillance project from three healthcare systems, which are located in the southwest, west side, and suburban southeast regions of Michigan. The population represented from the southwest region is widely dispersed and includes a smaller urban area with surrounding rural area. The west side region is mostly a large urban area with some surrounding rural area. The southeast region is a small suburban area outside a large city. Catchment areas were drawn around each healthcare system, considering distance and bed size of surrounding, competing healthcare facilities [MDCH, unpublished data], and the estimated catchment area populations were based on the 2000 U.S. Census. Prevalence for each healthcare system and its catchment area was estimated as the number of MRSA cases reported in 2005 divided by the estimated population of the catchment area. Confidence intervals were calculated based on the Poisson distribution. All statistical analyses were conducted using SAS® statistical software (SAS System for Windows V9.1.3, SAS Institute Inc., Cary, NC) and results were considered statistically significant if the p-value was <0.05.

Results

A total of 1,644 cases were analyzed, of which 937 (57%) were male. The race/ethnicity distribution was 993 (60%) white, 323 (20%) black, 67 (4%) "other" (i.e., Hispanic/Latino, American Indian/Alaskan Native, Asian, or Native Hawaiian/Pacific Islander), and 261 (16%) unknown. The mean age was 45 years old (s.d.=24 years). In this population, 661 (40%) were hospitalized during time of MRSA infection, 71 (4%) died during time of MRSA infection, 1,172 (71%) had at least one preexisting illness, while 281 (17%) were reported having no preexisting illnesses with 191 (12%) unknown.

There were 601 cases (37%) defined as HA-MRSA, 159 by PFGE and 442 by Predict (Table 4.1). The other 1,043 cases (63%) were defined as CA-MRSA, 85 by PFGE and 958 by Predict (Table 4.1). More males than females had CA-MRSA infections, yet this gender distribution was the same among HA-MRSA infections ($p<0.0001$). The higher proportion of whites was in the HA-MRSA group, but the higher proportion of blacks was in the CA-MRSA group ($p<0.0001$). The mean age for HA-MRSA infections was 65 years old (s.d.=19 years), and for CA-MRSA was 34 years old (s.d.=19 years) ($p<0.0001$). The highest proportions of HA-MRSA infections were reported among those 50 years and older, while the highest proportions of CA-MRSA infections were reported among those younger than 50 years old ($p<0.0001$) (Figure 4.1a). Figure 4.1b shows the number of reported MRSA infections age-adjusted according to 2000 U.S. Census data, and reveals very similar distribution curves for the HA- and CA-MRSA groups. Seventy-six percent of the individuals with HA-MRSA infections were hospitalized, while 20% with CA-MRSA were hospitalized during time of MRSA infection ($p<0.0001$). Of the individuals with HA-MRSA, 12% died during

time of MRSA infection compared to only 1% with CA-MRSA ($p<0.0001$). HA-MRSA infected individuals suffered from more preexisting illnesses than those with CA-MRSA, including diabetes mellitus, chronic renal insufficiency, dialysis ($p=0.0002$), cardiovascular disease, coronary heart failure, chronic obstructive pulmonary disease, and overall "any" preexisting illness (for each illness not previously specified, $p<0.0001$).

People with HA-MRSA infections were more likely to have been hospitalized >48 hours prior to the current infection, in an ICU >48 hours prior to the current infection, hospitalized in the previous year, had surgery in the previous year, received dialysis in the previous year, had a percutaneous device or indwelling catheter in the previous year, and/or resided in a LTC, nursing home or rehabilitation facility in the previous year compared to those with CA-MRSA (for each risk factor, $p<0.0001$). Of the five most common infection types analyzed, people with CA-MRSA were most likely to have skin or soft tissue infections ($p<0.0001$), while those with HA-MRSA suffered from bacteremia, pneumonia, and surgical site infections (for each infection type, $p<0.0001$). The proportion of individuals with "wound" infections did not differ significantly between the HA- and CA-MRSA groups ($p=0.479$). Of the non-β-lactam drugs evaluated, the HA-MRSA infected group was more likely to be resistant to ciprofloxacin, clindamycin, gentamicin, levofloxacin, and trimethoprim-sulfamethoxazole (for each drug, $p<0.0001$) compared to the CA-MRSA group.

The number of voluntarily reported MRSA infections by the patient's county of residence is shown in Figure 4.2. These numbers do not indicate prevalence or incidence as case submissions were voluntary, level of participation varied, and in some areas the laboratory, hospital, and/or health department staff dedicated extra effort to conduct

active surveillance for MRSA cases, therefore resulting in better reporting in those jurisdictions. Seventy-two percent of the MRSA infections were reported from hospital settings, followed by 18% from correctional facilities, and 6% from outpatient settings (Figure 4.3). Almost all of the HA-MRSA cases and close to two-thirds of the CA-MRSA cases were reported from hospital settings (92% and 61%, respectively). One-third of the CA-MRSA cases were reported from correctional facilities and outpatient settings (26% and 8%, respectively). Only two percent of all the MRSA case reports originated from local health departments, although, in many instances, the health department received initial MRSA infection reports from the other settings and dedicated much time and effort to assist with case follow-up.

Concordance/discordance of HA- or CA-MRSA classification by PFGE or Predict result versus classification by healthcare risk factor indicated that 376 (23%) of the MRSA infections would be classified differently (HA or CA) if the single classification variable healthcare risk factor were used instead of the new statistical classification model Predict result (311 cases) or PFGE result (65 cases) (Table 4.2). Results from the descriptive variables whose distributions by healthcare risk factor classification differ within HA/CA categories compared to classification by PFGE or Predict result are shown in Table 4.2a. There were 699 (43%) cases defined as HA-MRSA by healthcare risk factor and 945 (57%) cases defined as CA-MRSA. More MRSA infections were classified as HA using the healthcare risk factor categorization scheme. The group of 109 individuals that were classified as CA-MRSA by healthcare risk factor and HA-MRSA by Predict result has a higher proportion of whites (84%), a much older mean age ($\bar{x}$=60 years old), a higher proportion of hospitalized individuals (58%), a very low

proportion of skin and soft tissue infections (%23), and much higher resistance to ciprofloxacin, clindamycin, and levofloxacin (86%, 54%, 80%, respectively) compared to overall categorization as CA-MRSA by either healthcare risk factor or Predict result. The group of 202 individuals that were classified as HA-MRSA by healthcare risk factor and CA-MRSA by Predict result has a higher proportion of blacks (25%), a younger mean age ($\bar{x}$=41 years old), a much lower proportion of hospitalized individuals (27%), a similar proportion of hospitalizations in the previous year (62%), a very high proportion of skin and soft tissue infections (%77), and much lower resistance to ciprofloxacin, clindamycin, and levofloxacin (32%, 25%, 29%, respectively) compared to overall categorization as HA-MRSA by either healthcare risk factor or Predict result.

Data used to calculate the prevalence estimates for three Michigan healthcare systems and their catchment areas are presented in Table 4.3. Estimates of MRSA prevalence per 100,000 population indicate 94 for the southeast area, 196 for the southwest area, and 161 for the west side area.

Discussion

This study applied a new multivariable classification model to profile MRSA infections in the state of Michigan, and demonstrated the validity of this new method in the state. This model was previously developed using a subset of Michigan surveillance data that most closely approximated the PFGE categorization result. Data should be representative as they were collected from voluntary surveillance throughout Michigan, with some specific facilities and jurisdictions being more able and willing to participate than others. Reported cases represented a variety of locations including urban, suburban,

and rural areas, as well as healthcare settings (hospitals, outpatient clinics, LTC and rehabilitation facilities), correctional facilities, and local health departments. This sample should represent the entire Michigan population, allowing for broad characterization of HA- and CA-MRSA infections in this state. In three areas where all MRSA infections were consistently reported, estimation of MRSA prevalence was possible. Beyond the three specific areas, however, the voluntary nature of data collection for this surveillance makes estimation of prevalence and incidence rates of MRSA infections impossible for any particular reporting facility type, county, or statewide.

The HA- and CA-MRSA groups, as classified according to PFGE or Predict result, reveal recognized distributions for the demographic, clinical, and microbiologic variables that are consistent with those seen in previously published literature, according to the differing presentations of these two MRSA types [16, 17, 19, 20, 22-26]. The age means and distributions within the HA- and CA-MRSA groups were as previously reported. The number of reported Michigan CA-MRSA infections was highest among those ≤ 50 years (mean=34 years). This group would more likely be younger, healthier, and less likely to require healthcare services. Almost one-third of the CA-MRSA group reported having no preexisting illnesses. HA-MRSA increased as age group advanced from youngest to oldest, with the largest increase in number of reports occurring among individuals 40-49 years old and a progressive increase thereafter (mean=65). Similar distribution curves were seen after adjusting HA- and CA-MRSA infections by the number of Michigan residents within each age group. Older age increases the likelihood of comorbidities and illnesses, and therefore the possibility of more frequent interaction with healthcare facilities. Nearly all HA-MRSA cases had at least one preexisting illness,

and from one-fourth to two-fifths of this group reported having one or more of the six serious conditions listed in Table 4.1.

The proportion of males to females among the HA-MRSA reported infections was equal, whereas the proportion of males with CA-MRSA infections was significantly higher. These results correlate with previous studies reporting that a higher percentage of men are more likely to engage in "close contact" sports, have more cuts and skin abrasions, and live in close congregate settings like military barracks or correctional facilities, all previously established risk factors for CA-MRSA [10, 11, 13]. Other studies have reported higher prevalence of CA-MRSA infections among males in urban settings, men who have sex with men, and drug users [41-44].

The overall race/ethnicity distribution for this study population closely matches the race/ethnicity distribution of the Michigan population, with only a slightly lower proportion of whites and a slightly higher proportion of blacks. The race/ethnicity distribution for HA-MRSA infections closely corresponded to the state's population distribution. The CA-MRSA infection race/ethnicity distribution reveals a lower proportion of whites and higher proportion of blacks compared to the Michigan population. This finding coincides with other studies that have demonstrated an increased risk for CA-MRSA infections and colonization among blacks [34, 45-47]. The reason for this association remains unclear, but differences in immune response or socioeconomic factors (e.g., crowded living or decreased access to medical care), which are correlated with black race, may contribute to these findings [29, 48, 49].

Three-fourths of the HA-MRSA cases were hospitalized during time of MRSA infection compared to only one-fifth of the CA-MRSA cases. The CA-MRSA cases were

principally due to skin/soft tissue infections which are typically less serious if treated appropriately with wound care, incision and drainage, and/or antibiotics, when indicated. In contrast, almost half of HA-MRSA cases were associated with pneumonia, bacteremia, and surgical site infections, which often require hospitalization for appropriate treatment. The non-significant difference between the two groups for "wound" infections is likely due to the vagueness of the term, which is generically used to describe infections in both healthcare and community settings. Only a small proportion of the study population died during time of MRSA infection, although most of the deaths occurred among the more serious HA-MRSA infections (i.e., cases with bacteremia and pneumonia).

The HA-MRSA organisms had higher levels of multi-drug resistance compared to the CA-MRSA organisms, consistent with many previous studies [1, 2, 17, 21-24, 26]. Resistance was highest for two common fluoroquinolones, ciprofloxacin and levofloxacin, followed by resistance to clindamycin. Clindamycin resistance could potentially be even greater than revealed, since these data did not indicate how often tests were performed to identify the presence of inducible clindamycin resistance for erythromycin-resistant/clindamycin-susceptible isolates, and there was an overall high percentage of erythromycin resistance in this study population. The continual acquisition of resistance genes by HA-MRSA organisms is of serious concern and establishes the real possibility of a pan-resistant MRSA organism. This concern came even closer to realization with the report of the first HA-MRSA organism to also acquire resistance to vancomycin (VRSA) in 2002, followed by six additional cases through 2006 (Sievert, et al, March 2008, Chapter V). This concern emphasizes the importance of judicious use of

antimicrobials and the need for the introduction of new antimicrobial classes or a vaccine against MRSA.

CA-MRSA infections identified within healthcare settings have been reported in recent years [50-52]. Sixty-one percent of the reported Michigan CA-MRSA infections were reported from hospital settings. These findings highlight the significant disease burden that such community infections place on the emergency departments and possibly inpatient units of healthcare facilities, also increasing the likelihood for transmission of CA-MRSA within such settings. Correctional facilities also had a high burden of CA-MRSA infections. These settings are a recognized as sites for acquisition and transmission of CA-MRSA [7-9, 11]. CA-MRSA infections in correctional facilities also contribute to transmission in the surrounding communities due to high volumes and continual movement of individuals between these two settings. Individuals in correctional settings also increase the likelihood for transmission of CA-MRSA within healthcare facilities as they utilize medical services [46].

Three classification variables have been commonly used to define MRSA infections as HA or CA: healthcare risk factor, infection type, and susceptibility pattern. Healthcare risk factor was not included in the new multivariable model that generated the Predict result. The comparisons of HA and CA categorizations by Predict result versus healthcare risk factor indicate that of the 109 cases classified as CA-MRSA by healthcare risk factor and HA-MRSA by the multivariable model, many are probably not true CA-MRSA, but are HA-MRSA cases misclassified according to the healthcare risk factor scheme due to missing healthcare risk factor data. Some cases may be true CA-MRSA misclassified by the multivariable model as HA-MRSA due to older age, being

hospitalized, and having more serious infections. Of the 202 cases classified as HA-MRSA by healthcare risk factor and CA-MRSA by the multivariable model, many are probably not true HA-MRSA, but are CA-MRSA cases misclassified according to the healthcare risk factor scheme due to a history of hospitalization in the previous year. Some cases may be true HA-MRSA misclassified by the multivariable model as CA-MRSA due to younger age and not being hospitalized. There is also the possibility that some of the 202 cases are the CA-MRSA strain acquired in the healthcare setting. Categorization by the Predict result calculated from the new statistical model considers multiple variables (infection type, susceptibility pattern, age, and hospitalized), and therefore more accurately classifies the cases as HA- or CA-MRSA. These results underscore some important messages; individuals in Michigan may be more likely to acquire CA-MRSA from their community than HA-MRSA from brief interactions with healthcare facilities, acquisition of CA-MRSA from interactions with healthcare facilities may be likely, and the new multivariable classification model is an accurate method of classifying HA- and CA-MRSA infections. For now, HA- and CA-MRSA are distinguishable from one another by molecular make-up, including resistance levels and the types of infections each causes. This scenario allows the multivariable model to serve as a proxy measure of HA and CA infections, without having to collect data on healthcare risk factors, which is often difficult to obtain accurately. Collecting data on healthcare and community risk factors will, however, become necessary and important to accurately classify MRSA infections as HA or CA, if the USA300 strain becomes the most prevalent MRSA strain within healthcare settings.

Results reveal varying prevalence estimates for all three of the healthcare systems and their catchment areas (Table 4.3). These are only estimates and do not fully represent an entire region, or specific delineated areas of Michigan. MRSA is a statewide problem and causes a considerable number of infections throughout Michigan. Although we believe that the numerators accurately represent all cases of MRSA infections from the three healthcare systems for 2005, the denominators are only approximate estimates of population market share in areas where many healthcare facilities from different systems are in close proximity to one another and compete for overlapping populations of individuals. The MRSA prevalence estimates vary between the healthcare system areas, but the racial distributions from their catchment areas are quite similar. Further surveillance is needed to obtain more thorough data from a larger number of healthcare systems, in order to more accurately estimate the true prevalence of MRSA throughout Michigan and to be able to account for any differences between areas.

The voluntary MRSA surveillance conducted from the fourth quarter of 2004 through the end of 2005, allowed for this first comprehensive epidemiologic profile of MRSA infections in Michigan. The newly developed multivariable statistical classification model provided the ability to more accurately classify these MRSA infections as healthcare- or community-associated in the absence of PFGE result. It is clear that MRSA infections are prevalent throughout the variety of geographic areas of Michigan. The groups at highest risk for acquisition of HA- and CA-MRSA infections and the settings in most need of targeted interventions are not unique compared to other areas of the US. However, this Michigan-specific data highlights areas of concern for the state. In particular, results suggest the need to create specific CA-MRSA prevention

efforts to target correctional facilities, especially jails where individuals remain for shorter periods of time and then are released back into the communities. These results also indicate that a large number of CA-MRSA infections are reported from hospital settings, and these infections may not stop at the emergency department doors. Therefore, Michigan hospitals need to tailor infection control and prevention efforts to address both HA- and CA-MRSA organisms, and ensure that surveillance of resistant organisms in these settings are capable of identifying further changes in resistant *S. aureus* organisms.

The Michigan MRSA profile will continue to evolve, and control efforts and educational prevention messages must keep up with the changing epidemiology, in order to effectively combat these adept organisms. To this end, it is crucial that public health efforts to track and characterize these organisms continue.

Acknowledgements

We thank all of the Michigan public health professionals, laboratorians, infection preventionists, and health care providers who dedicated extra time and effort to collect and report these important MRSA data. We also thank David Dixon and the MDCH Houghton Laboratory for isolate collection and PFGE testing, Steve Cali for his diligent data entry efforts, and Ed Hartwick for his invaluable GIS ideas and support.

Table 4.1. Michigan MRSA Infections Classified as Healthcare-Associated (HA) or Community-Associated (CA) by PFGE Result (n=244) or Predict Result (n=1,400).

Demographic/Characteristic	Healthcare-Associated	Community-Associated	*p*-value*
Total N=1,644	N=601 (37%) n (%)	N=1,043 (63%) n (%)	
Gender: Male	302 (50)	635 (61)	<0.0001
Race: White	406 (80)	587 (67)	<0.0001
Black	80 (16)	243 (28)	
Other	20 (4)	47 (5)	
Age 0-80+	597 ($\bar{x}$=65 s.d.=19)	1,040 ($\bar{x}$=34 s.d.=19)	<0.0001
Hospitalized: Yes	453 (76)	208 (20)	<0.0001
Survival: Died	64 (12)	7 (1)	<0.0001
Preexisting Illness(s):			
None	25 (4)	256 (29)	<0.0001
Diabetes Mellitus	227 (39)	82 (9)	<0.0001
Chronic Renal Insufficiency	94 (16)	17 (2)	<0.0001
Dialysis	25 (4)	11 (1)	0.0002
Cardiovascular Disease	163 (28)	56 (6)	<0.0001
Coronary Heart Failure	139 (24)	22 (2)	<0.0001
COPD	147 (25)	34 (4)	<0.0001
Any Underlying Illness	549 (96)	623 (71)	<0.0001
Healthcare Risk Factors:			
Hospitalized >48 hours	103 (17)	30 (3)	<0.0001
In ICU >48 hours	55 (9)	11 (1)	<0.0001
Hospitalized in Prior Year	321 (53)	156 (15)	<0.0001
Surgery in Prior Year	185 (31)	96 (9)	<0.0001
Dialysis in Prior Year	33 (5)	14 (1)	<0.0001
Indwell Device in Prior Yr	185 (31)	62 (6)	<0.0001
LTC/Rehab in Prior Year	187 (31)	45 (4)	<0.0001
Infection Type: Bacteremia	73 (12)	15 (1)	<0.0001
Pneumonia	150 (25)	17 (2)	<0.0001
Skin / Soft Tissue	78 (13)	908 (88)	<0.0001
Surgical Site	47 (8)	11 (1)	<0.0001
Drug Resistance:			
Ciprofloxacin	178 (94)	97 (27)	<0.0001
Clindamycin	344 (78)	103 (15)	<0.0001
Gentamicin	54 (10)	8 (1)	<0.0001
Levofloxacin	525 (92)	204 (24)	<0.0001
Trimeth.-Sulfamethoxazole	16 (3)	4 (0.4)	<0.0001

*p-values shown are from χ^2 tests for categorical variables and t-test for Age.

Figure 4.1a. Age Group Distribution for Michigan MRSA Infections Classified as Healthcare-Associated (HA) or Community-Associated (CA) by PFGE Result (n=244) or Predict Result (n=1,400).

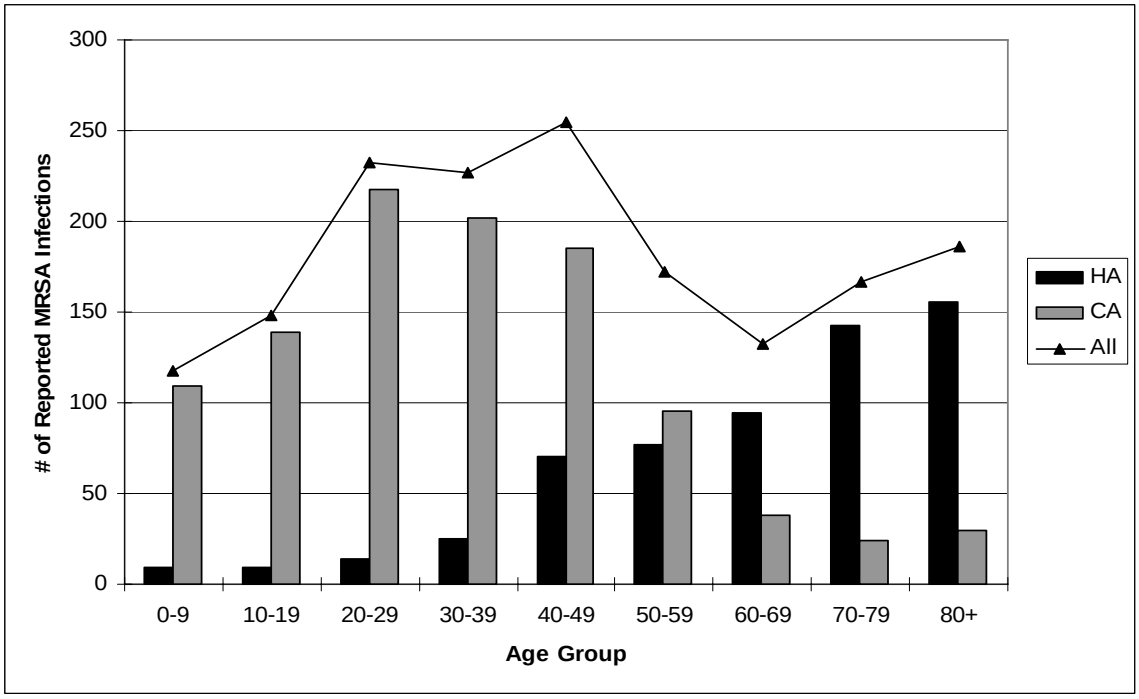


Figure 4.1b. Age-Adjusted Rate Distribution of Reported Michigan MRSA Infections Classified as Healthcare-Associated (HA) or Community-Associated (CA) by PFGE Result (n=244) or Predict Result (n=1,400).

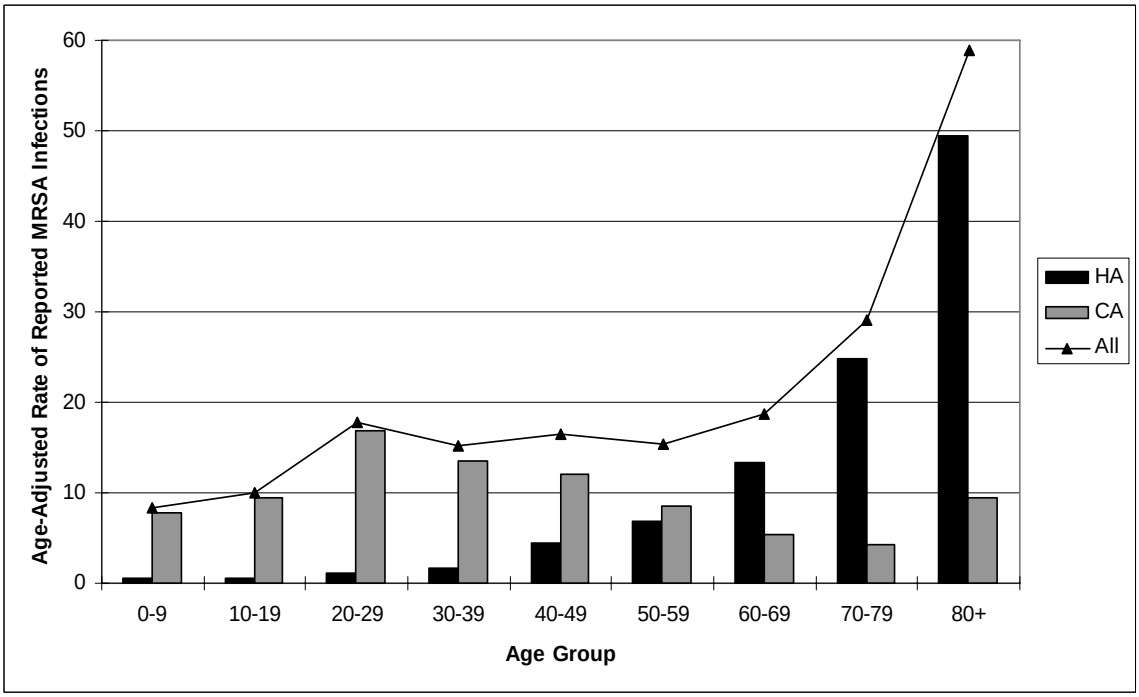
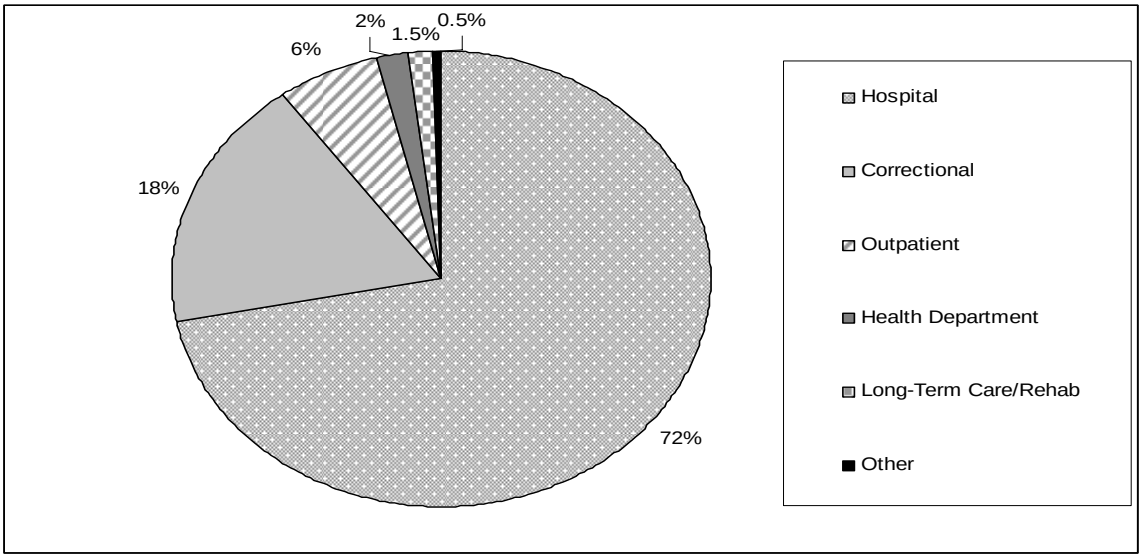
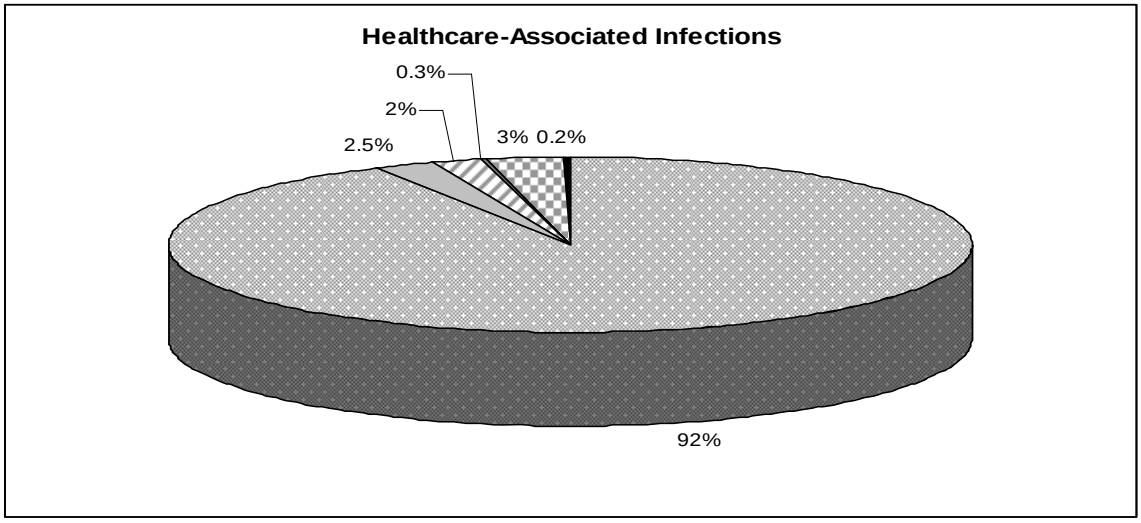


Figure 4.2. Number of Michigan MRSA Infections Voluntarily Reported by Patient County of Residence.

Figure 4.3. Michigan MRSA Infections by Reporting Facility Type and Classified as Healthcare-Associated (HA) or Community-Associated (CA) by PFGE Result (n=244) or Predict Result (n=1,400).





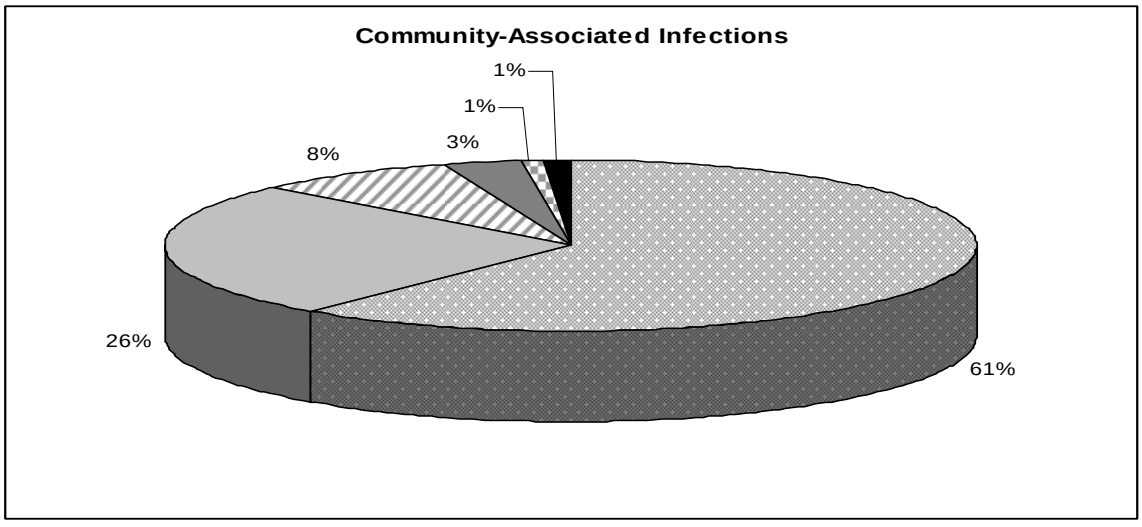


Table 4.2. Comparison of Michigan MRSA Infections Classified as Healthcare-Associated (HA=1) or Community-Associated (CA=0) by PFGE Result (n=244) and Predict Result (n=1,400) or by Healthcare Risk Factor (n=1,644).

	PFGE Results	**Predict Results**	**Healthcare Risk Factor Results**	**# of Cases Matching Row Combination Results [n, %]**
Concordant	1		1	129 (8)
		1	1	333 (20)
	0		0	50 (3)
		0	0	756 (46)
			Total:	**1,268 (77%)**
Discordant	1		0	30 (2)
		1	0	109 (7)
	0		1	35 (2)
		0	1	202 (12)
			Total:	**376 (23%)**
			Total:	**1,644 (100%)**

Table 4.2a. Results from Healthcare Risk Factor Classification as Healthcare-Associated (HA) or Community-Associated (CA) MRSA that Differ Compared to Classification by PFGE Result and Predict Result.

Demographic/Characteristic	Healthcare-Associated	Community-Associated	*p*-value*
Total N=1,644	N=699 (43%) n (%)	N=945 (57%) n (%)	
Race: White	453 (76)	540 (69)	0.015
Black	118 (20)	205 (26)	
Other	27 (4)	40 (5)	
Age 0-80+	695 ($\bar{x}$=58 s.d.=23)	942 ($\bar{x}$=35 s.d.=21)	<0.0001
Hospitalized: Yes	442 (63)	219 (23)	<0.0001
Infection Type: Skin / Soft Tissue	217 (31)	769 (83)	<0.0001
Drug Resistance:			
Ciprofloxacin	162 (75)	113 (34)	<0.0001
Clindamycin	322 (67)	125 (19)	<0.0001
Levofloxacin	487 (77)	242 (31)	<0.0001

*p-values shown are from χ^2 tests for categorical variables and t-test for Age.

Table 4.3. Approximate Prevalence Estimates for Three Healthcare Systems and Their Catchment Areas in Michigan, 2005.

Michigan Area of Reporting Healthcare System	MRSA Cases Reported from Healthcare System	Estimated Population Surrounding Healthcare System	MRSA Prevalence per 100,000 population (95% Confidence Intervals)*
Southeast suburb	202	215,769	94 (85-109)
Southwest	262	133,765	196 (185-223)
West side	586	363,602	161 (148-167)

* Confidence Intervals calculated using Poisson distribution.

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Chapter V

Vancomycin-Resistant *Staphylococcus aureus* in the United States, 2002-2006

Abstract

Background: This report compares the clinical characteristics, epidemiologic investigations, infection control evaluations, and microbiologic findings of all seven of the cases of vancomycin-resistant *Staphylococcus aureus* (VRSA) infection in the United States during the period 2002-2006.

Methods: Epidemiologic, clinical, and infection control information was collected. VRSA isolates underwent confirmatory identification, antimicrobial susceptibility testing, pulsed-field gel electrophoresis, and typing of the resistance genes. To assess VRSA transmission, case-patients and their contacts were screened for VRSA carriage.

Results: Seven cases were identified from 2002 through 2006; five were reported from Michigan, one was reported from Pennsylvania, and one was reported from New York. All VRSA isolates were *vanA*-positive and had a median vancomycin minimum inhibitory concentration of 512 µg/mL. All case patients had a history of prior methicillin-resistant *S. aureus* and enterococcal infection or colonization; all had several underlying conditions, including chronic skin ulcers; and most had received vancomycin therapy prior to their VRSA infection. Person-to-person transmission of VRSA was not

identified beyond any of the case-patients. Infection control precautions were evaluated and were consistent with established guidelines.

Conclusions: Seven patients with *vanA*-positive VRSA have been identified in the United States. Prompt detection by microbiology laboratories and adherence to recommended infection control measures for multidrug-resistant organisms appear to have prevented transmission to other patients.

Introduction

Staphylococcus aureus and *Enterococcus* spp. are gram-positive, human commensal bacteria. *S. aureus* is commonly found on the skin and in the nares of healthy people. Enterococci are normally present in the human intestines. Both of these bacteria are opportunistic pathogens and have been among the most common causes of nosocomial infections [1,2]. During the past two decades these bacteria have developed resistance to commonly prescribed antimicrobial agents. Methicillin-resistant *S. aureus* (MRSA) infections first emerged in the U.S. in the 1970s, and by the 1990s MRSA was considered endemic in most large urban medical centers [3,4]. Vancomycin-resistant enterococci (VRE) were first reported in a U.S. hospital in 1989, and rapidly became a common cause of healthcare-associated infections [5-7]. Although vancomycin could no longer be used to treat the growing number of VRE infections, it remained the only uniformly effective antimicrobial agent to treat the numerous MRSA infections [8-10]. In 1992, Noble et al. [11] demonstrated that conjugal transfer of the *vanA* gene, which mediates vancomycin resistance, from VRE to MRSA on the skin surface of hairless mice could be achieved, creating vancomycin-resistant *S. aureus* (VRSA). In an era of increasing rates of VRE and MRSA infection, the prospect of this transfer occurring spontaneously in vivo was of serious concern. In 1997, the first vancomycin-intermediate *S. aureus* (VISA) infection was reported from Japan [12]. However, the mechanism of resistance was not mediated by *vanA* but rather by a change in cell physiology due to genetic mutations and altered expression of certain genes, resulting in a characteristic thickened cell wall that prevents vancomycin from reaching its target [13,14].

In June 2002, the Michigan Department of Community Health reported the first clinical case of *vanA*-mediated VRSA in the world [15,16]. Since then, six additional cases have been confirmed by the Centers for Disease Control and Prevention (one case each from Pennsylvania and New York and five cases from Michigan) [17-21]. Information regarding only the first three cases has been published. This report will compare the clinical characteristics, epidemiologic investigations, infection control evaluations, and microbiologic findings of all seven documented cases of VRSA infection in the world.

Methods

Patients and Medical History

A patient with VRSA infection was defined as an individual from whom an *S. aureus* isolate was recovered for which the vancomycin MIC was ≥32 μg/mL before 2006 and ≥16 μg/mL after the vancomycin breakpoint was changed in 2006 [22-24]. Information regarding medical history, clinical course, treatment modalities (including antimicrobial and surgical therapy), and outcome was obtained through medical record review and interviews with patients, close family and friends, and medical personnel.

Epidemiologic Investigations

A comprehensive epidemiologic contact investigation was conducted for each case-patient with VRSA infection and their contacts. Specimens were collected from the nares, axilla, groin, wounds, and rectum of each case-patient to determine both VRSA and VRE colonization status. To assess the extent of transmission beyond the case-patients, nares, skin wound, and catheter exit site swab specimens were collected from all

available patient contacts during the period of transmissibility. This period was defined as the time from the last date of culture negative for VRSA through the date that appropriate infection control precautions were implemented following the isolation of VRSA. Places where the cases resided or visited within the period of transmissibility were identified as facilities where transmission could have occurred. These facilities included patient homes, hospitals, rehabilitation and long-term-care facilities, physician offices, dialysis centers, an infusion center, a wound care clinic, and a nail salon. Patient contacts considered to be at risk for transmission included people who had direct physical contact with patients, shared the same living space, or had the same healthcare providers during the period of transmissibility. Persons who worked in laboratories where VRSA organisms were initially identified were also considered to be at risk. Overall, at-risk individuals included physicians, nurses, therapists, other patients, family members, friends, laboratory technologists, and a manicurist. On-going surveillance cultures were performed for the case-patients and all individuals who remained at risk because of direct patient contact throughout the investigations.

Infection Control Policies and Procedures

Infection control policies and procedures were assessed in all healthcare facilities where the patients with VRSA had received care during their periods of transmissibility. These assessments were conducted through interviews with infection control supervisors, review of written procedures, and direct observation of healthcare worker practices.

Laboratory Procedures

Isolate identification and antimicrobial susceptibility testing were conducted at local clinical laboratories and then confirmed at state health department laboratories.

VRSA isolates were then sent to the Centers for Disease Control and Prevention (Atlanta, GA) for further characterization. Species identification was determined using standard biochemical and molecular methods [25]. Antimicrobial susceptibility testing was performed using the reference broth microdilution method according to the Clinical and Laboratory Standards Institute [22-24]. Genomic DNA from VRSA isolates was isolated by the silica-gel membrane method (Qiagen DNeasy) and was used as a template for the polymerase chain reaction (PCR) to detect the presence of *mecA*, *vanA*, *vanB*, *vanC*, and *vanD* [26-28]. Pulsed-field gel electrophoresis (PFGE) was performed using *Sma*I-digested DNA from VRSA isolates, and banding patterns were analyzed and classified as described elsewhere [29]. All isolates underwent typing of the staphylococcal cassette chromosome *mec* (SCC*mec*) genetic element using PCR [30].

Results

Case Descriptions

Five (71%) of the seven cases of VRSA infection were reported from Michigan (Table 5.1). Four (57%) of the seven case-patients with VRSA infection were female, five (71%) were white, and the median age was 58 years [range: 40-78 years]. All seven case-patients had a history of previous MRSA and enterococcal (four with VRE) infections or colonization. Most case-patients had several underlying conditions, including five patients (71%) with chronic skin ulcers, four (57%) with diabetes, and three (43%) with chronic renal failure; two (29%) were considered obese. One of the case-patients (patient 2) had not received vancomycin therapy during the 5 years prior to VRSA infection, one had not received vancomycin therapy during the previous 4 months

(patient 3), four had received vancomycin for 5-9 weeks in the previous three months, and one had intermittently received vancomycin for approximately ten years. VRSA was isolated from specimens of either ulcers or wounds for six (86%) of the case-patients and from urine specimens from a nephrostomy tube for the other case-patient. In all but one case-patient (patient 3), specimen collection was prompted by a wound or ulcer that appeared infected or was healing (in patient 5). Enterococcal species were recovered from the sites from which specimens were culture positive for VRSA for five of the seven case-patients; three of the isolates were VRE. All culture specimens were polymicrobial and included a variety of gram-negative organisms. At the time of specimen collection, four case-patients (57%) were inpatients, two (29%) were outpatients, and one (14%) was a long-term care resident. Case-patients were observed for a median of 10 weeks (range: 5-56 weeks) after initial VRSA isolation. Follow-up was concluded after cultures results remained negative for VRSA for at least three consecutive weeks without antimicrobial therapy, when the culture site healed, or at the time of death. One case-patient persistently tested positive for VRSA, and six case-patients became culture-negative for VRSA following multimodal therapy, including wound-care (n=6), surgical intervention (n=5), and antimicrobial therapy (n=5).

Epidemiologic Investigation Results

Two case-patients were colonized with VRSA at body sites other than the initial culture sites; one case-patient (patient 5) had VRSA isolated from a specimen from the groin, adjacent to the VRSA-infected wound site, and one case-patient (patient 6) had VRSA isolated from a specimen from the nares. After showering with chlorhexidine for five days (patient 5) and using nasal mupirocin twice daily for five days (patient 6),

VRSA was not recovered again from either site. VRE isolates (five *E. faecalis* and one *E. faecium*, one patient was colonized with both) were recovered from specimens from a wound, nephrostomy tube, or gastrointestinal tract for five (71%) of the case-patients.

The median number of case-patient contacts from whom surveillance cultures for VRSA were performed was 42 (range: 23-371 case-patient contacts) (Table 5.2). Fourteen percent to 30% of case-patient contacts were colonized with methicillin-susceptible *S. aureus* (MSSA), 3%-8% were colonized with MRSA, but none were colonized with VRSA.

Infection Control Findings

Standard infection control precautions were in place at all of the involved healthcare facilities prior to identification of the cases of VRSA infection, and the policies and practices were appropriate for the respective settings. Prior to recovery of VRSA, most case-patients had known MRSA infection or colonization; therefore, contact precautions were being used. Once VRSA was identified, contact precautions were reinforced and some enhanced measures were instituted at all facilities and for all staff having continued contact with the infected patients. For inpatients, the enhanced precautions included placing case-patients in private rooms. For outpatients, treatment was administered in dedicated rooms or areas separate from other patients and during the last appointment of the day. For all patients, enhanced measures included dedicated staff and equipment, new gloves and gowns for each patient interaction, masks with eye protection when the potential for splashing/spraying of infectious material existed (e.g., during wound care in the podiatry clinic for patient 1), and thoroughly cleaning and disinfecting all patient rooms and equipment after each use and after discharge from the

hospital. Enhanced contact precautions remained in place throughout the follow-up period for both inpatients and outpatients. Follow-up was discontinued if culture results remained negative for VRSA for at least three consecutive weeks without antimicrobial therapy or the primary culture site healed. However, contact precautions remained in place if outpatient care continued.

Laboratory Results

The seven VRSA isolates had a median vancomycin MIC of 512 μg/mL [range: 32 to 1024 μg/mL] (Table 5.3). All isolates tested susceptible to five or more antimicrobial agents approved by the Food and Drug Administration (FDA) for treating *S. aureus* infection including linezolid, quinupristin/dalfopristin , and trimethoprim/sulfamethoxazole; six isolates were susceptible to daptomycin. All of the isolates acquired a *vanA*-containing Tn*1546*-like element by independent genetic events [15,21,31]. In each isolate the *vanA* gene was localized to a plasmid, which ranged in size from 40 to 120 kb. Five isolates belonged to MRSA lineage USA100 and contained SCC*mec* type II and one belonged to MRSA lineage USA800 and contained SCC*mec* type IV. The VRSA isolate from patient 6 did not belong to any current PFGE type in the database, and the SCC*mec* type could not be determined using standard primers.

Discussion

This report describes the clinical and laboratory characteristics of seven patients from whom *vanA*-containing VRSA isolates were recovered. Most of these patients had several characteristics in common including chronic underlying conditions, history of MRSA and VRE infection or colonization, and previous exposure to vancomycin. All but

two patients had VRE recovered at the time of VRSA isolation, either from the culture site or a rectal specimen. One of the two patients that did not present with VRE infection or colonization at the time when VRSA was identified did have a history of cultures positive for VRE; the other patient had a history of cultures positive for *Enterococcus* species, but unfortunately, susceptibility testing was never conducted. It is thought that, in all instances, VRE strains likely donated the *vanA* gene to *S. aureus* strains within a polymicrobial biofilm (e.g., wound, nephrostomy tube, or gastrointestinal tract) [15,21]. The transferred *vanA* gene was able to be maintained in the *S. aureus* strains, even without the continued presence of VRE and vancomycin.

Although most of the case-patients exhibited superficial signs of infection at the culture sites, none developed systemic signs or symptoms. This lack of systemic involvement may explain the low attributable morbidity and mortality. However, a recent study by Fox et al. [32] demonstrated these strains were highly virulent in an experimental endocarditis rabbit model, have the ability to cause significant disease, and should be treated promptly when isolated. Currently, not enough data are available to recommend a standard treatment regimen for VRSA infection. All of the VRSA isolates were susceptible to a number of FDA-approved antimicrobial agents, and a recent study of experimental endocarditis using the first Michigan VRSA strain and a recent in vitro study using the VRSA strain from New York suggest that therapy with a synergistic combination of vancomycin plus a β-lactam may be an option [32,33]. In addition to the variety of antimicrobials used as therapies for the VRSA infections, it is notable that surgical debridement and wound care were important treatment modalities in this case series.

Although researchers have been unable to demonstrate in vitro transfer of *vanA* from the VRE strains obtained from these VRSA case-patients to *S. aureus* strains, conjugal transfer of *vanA* plasmid from VRSA strains to *vanA*-negative *S. aureus* strains has been demonstrated [15]. This suggests that, once the initial conjugal transfer of *vanA* from VRE strains to *S. aureus* strains occurs, the spread of *vanA* between *S. aureus* strains might be more likely. Therefore, to ensure implementation of infection control precautions to prevent transmission, clinical microbiology laboratories need to issue prompt notification of a potential VRSA isolate to infection control personnel [34,35]. In addition, the extent of transmission that could occur before infection control precautions are implemented should be assessed. Guidance has been developed to assist in developing a plan for this contact investigation [35]. To date, no transmission of VRSA beyond any of the case-patients reported here has been identified.

One of the most prominent, outstanding questions is why five of the seven cases of VRSA infection occurred in Michigan. This regional emergence likely occurred because of the convergence of several factors, including population characteristics, antimicrobial pressure, and the presence of VRE strains that are more likely to donate *vanA* operon. Michigan has a large population of individuals with chronic underlying conditions, such as diabetes and end-stage renal disease, both of which are conditions that appear associated with these infections. It is estimated that 590,000 adults (7.8% of the adult population) in Michigan have received diagnoses of diabetes [36]. Often patients with diabetes develop other chronic health conditions, including impaired sensation in the feet, leading to unrecognized injuries (such as foot ulcers) from which VRSA has been isolated. In addition, diabetes is also the leading cause of end-stage renal disease.

Compared with other states, Michigan has the eighth highest prevalence of diabetes, the ninth highest incidence of end-stage renal disease, and the ninth greatest number of dialysis and transplant facilities [37]. Patients receiving dialysis are at high risk for infection with invasive MRSA, leading to increased vancomycin exposure and, because of their reduced renal clearance of the drug, prolonged exposure to subtherapeutic levels of vancomycin. A recent report noted that the rate of invasive MRSA infections among patients receiving dialysis is higher than that among any other known patient population and is 100 times higher than that among the general population [38]. In addition to these patient population factors, Michigan was one of the first locations in the United States to document MRSA occurring outside of healthcare facilities in the 1980s [39]. Therefore, the early use of vancomycin in Michigan for treatment of these MRSA infections may have provided increased selective pressure for the development of vancomycin-resistant organisms.

The demographic characteristics and risk factors of Michigan's population may favor the emergence of VRSA, yet other regions have similar populations and have not witnessed this emergence. Therefore, specific characteristics of either the *S. aureus* or VRE strains circulating in Michigan may lead to a greater propensity for them to donate and/or acquire *vanA*. While each VRSA strain has been distinct, the associated VRE strains from the Michigan patients contain a broad host-range Inc-18 conjugative plasmid that may be more likely to donate *vanA* to other bacterial species, compared with VRE strains from other regions [31,40]. Studies are currently underway to examine the prevalence of these plasmids within enterococcal isolates from Michigan and nationally.

In summary, VRSA infection continues to be a rare occurrence. A few specific existing factors seem to have predisposed these case-patients to VRSA infection, including prior MRSA and enterococcal infections or colonization, underlying conditions (such as chronic skin ulcers and diabetes), and previous treatment with vancomycin. Further studies are necessary to investigate the specific characteristics of the *S. aureus* and VRE plasmids isolated from these case-patients. Appropriate antimicrobial prescribing by healthcare providers, adherence to recommended infection control guidelines, and ultimately, the control of both MRSA and VRE are necessary to prevent further emergence of VRSA strains.

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Table 5.1. Clinical Aspects of Vancomycin-Resistant *Staphylococcus aureus* Infections in Patients from the United States, 2002-2006.

Case	Date	State	Age (years)	Sex	Culture Source/Diagnosis	Underlying Conditions	VAN Exposure (weeks in prev 3 mos)	Therapy	Outcome	Ref(s)
1	June 2002	MI	40	Female	Central venous catheter exit site, catheter-tip, and plantar ulcers/ Suspected exit-site infection and plantar soft-tissue infection	Diabetes, chronic renal failure requiring hemodialysis	6.5	Catheter removed, SXT (2 weeks post-op), surgical debridement of ulcers and twice per week evaluation with debridement, application of gentian violet and contact casts	Both culture sites cleared (Last VRSA positive culture in Aug.) Follow-up continued through Nov. (20 weeks). Foot ulcers healed in December 2002	15, 16
2	Sept. 2002	PA	70	Male	Plantar ulcer/ Cellulitis along plantar fascia and polymicrobial osteomyelitis of the right calcaneous	Obesity with multiple lower extremity ulcers, osteomyelitis, and status-post amputation	0 (last Sept. 1997)	LNZ (stopped after 4 weeks due to thrombocytopenia), PTZ and SXT (6 weeks), daily chlorhexidine washes for 2 weeks, wound care	VRSA not recovered again after initiation of antimicrobial therapy. Ulcer was healing when patient died 11 weeks after isolation of VRSA. Death was attributable to underlying diseases.	17, 18
3	March 2004	NY	63	Female	Urine via nephrostomy tube and nephrostomy exit-site/ Cloudy urine, no systemic symptoms	Advanced stage of multiple sclerosis, diabetes, recurrent UTIs, kidney stones, nephrostomy tube, gastrostomy tube	0 (last Nov. 2003)	LEV (10 days)	Persistently culture pos for VRSA. Admitted for SOB rule out pneumonia, blood positive for *Morganella*, died during admission April 2005	19, 20, 21
4	Feb. 2005	MI	78	Male	Toe wound/ Gangrene of the second toe	Non-insulin diabetes, coronary artery disease, peripheral vascular disease, chronic renal failure, obstructive uropathy, aortic valve replacement (Oct. 2004)	9	Gangrenous toe amputation (Feb. 2005), LNZ and RIF (3.5 weeks), wound care	Toe wound cultured weekly for 7 weeks, no VRSA detected. Follow-up discontinued mid-April 2005	NA

5	Oct. 2005	MI	58	Female	Surgical site wound/Post-op panniculectomy and ventral hernia repair surgical site infection	Morbid obesity, hypertension, asthma, chronic bronchitis, arthritis	8	No antimicrobial therapy, debridement, Wound Vacuum therapy	Groin colonization, chlorhexidine showers 5 days. No subsequent wound or surveillance cultures recovered VRSA (5 weeks). Wound healed (Feb 2006)	NA
6	Dec. 2005	MI	48	Male	Two non-healing plantar ulcers/ Plantar soft-tissue infection and osteomyelitis of the right lower limb	MVA (1981) open fracture of tibia and fibula, compartment syndrome and osteomyelitis following leg-lengthening surgery (1995), non-healing foot ulcers	~10 years to control acute occurrences of infection	DAP (4 weeks), debridement and wound care, BKA (May 2006)	Nasal colonization, mupirocin decolonization (BIDX5 days). Subsequent cultures VRSA negative (10weeks).	NA
7	Oct. 2006	MI	43	Female	Triceps wound/ Necrotizing fasciitis of the right upper limb	Diabetes, chronic renal failure requiring hemodialysis, multiple extremity ulcers, chronic diarrhea	5	LNZ and ETP (2 weeks), wound care	VRSA not recovered again after wound debridement and initiation of antimicrobial therapy. Follow-up discontinued after 8 weeks. Wound healing.	NA

Abbreviations are as follows: DAP, daptomycin; ETP, ertapenem; LEV, levofloxacin; LNZ, linezolid; PTZ, piperacillin-tazobactam; RIF, rifampin; SXT, trimethoprim-sulfamethoxazole; VAN, vancomycin; UTIs, urinary tract infections; SOB, shortness of breath; MVA, motor vehicle accident; BKA, below knee amputation; BID, twice a day, Ref(s), References, NA, Not Applicable.

Table 5.2. Contact Investigation Results of Vancomycin-Resistant *Staphylococcus aureus* Cases from the United States, 2002-2006.

Case	Date	State	Total Contacts Cultured	MSSA Colonization (N, %)	MRSA Colonization (N, %)
1	June 2002	MI	371	82 (22%)	28 (8%)
2	Sept. 2002	PA	262	74 (28%)	21 (8%)
3	March 2004	NY	101	NA	NA
4	Feb. 2005	MI	35	5 (14%)	1 (3%)
5	Oct. 2005	MI	23	NA [7 (30%) *S. aureus*]*	NA
6	Dec. 2005	MI	42	10 (24%)	2 (5%)
7	Oct. 2006	MI	38	6 (16%)	2 (5%)

Abbreviations are as follows: MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*.
*At the request of the facility, methicillin/oxacillin susceptibility testing was not conducted on these 7 *S. aureus* isolates.

Table 5.3. Laboratory Aspects of Vancomycin-Resistant *Staphylococcus aureus* Infections in Patients from the United States, 2002-2006.

Case	PFT	SCCmec	Minimum Inhibitory Concentration, µg/ml (Interpretation)													
			CC	DAP	ERY	GM	OXA	LEV	LNZ	PEN	Q/D	RIF	SXT	TEC	TET	VAN
1	USA100	II	>8 (R)	0.5 (S)	>8 (R)	64 (R)	>16 (R)	16 (R)	2 (S)	>2 (R)	≤1(S)	>8 (R)	0.25 (S)	32 (R)	1(S)	1024 (R)
2	USA100	II	>8 (R)	0.5 (S)	>8 (R)	64 (R)	>16 (R)	16 (R)	2 (S)	>2 (R)	≤1 (S)	≤0.25 (S)	0.25 (S)	8 (S)	>16 (R)	32 (R)
3	USA800	IV	>8 (R)	0.5 (S)	>8 (R)	32 (R)	>16 (R)	16 (R)	2 (S)	>2 (R)	≤1 (S)	≤0.25 (S)	0.25 (S)	16 (I)	>16 (R)	64 (R)
4	USA100	II	>16 (R)	≤0.5 (S)	>8 (R)	≤2 (S)	>16 (R)	>16 (R)	2 (S)	≥2 (R)	0.5 (S)	≤0.5 (S)	0.25 (S)	16 (I)	≤1(S)	256 (R)
5	USA100	II	>16 (R)	≤0.5 (S)	>8 (R)	≤2 (S)	>16 (R)	>16 (R)	4 (S)	>2 (R)	2 (I)	≤0.5 (S)	0.25 (S)	8 (S)	≤1(S)	512 (R)
6	Not Defined	Non-typable	>16 (R)	1 (S)	>8 (R)	≤2 (S)	>16 (R)	>16 (R)	2 (S)	>2 (R)	1 (S)	≤0.5 (S)	0.25 (S)	16 (I)	≤1(S)	1024 (R)
7	USA100	II	>16 (R)	2 (NS)	>8 (R)	≤2 (S)	>16 (R)	8 (R)	2 (S)	>2 (R)	0.5 (S)	≤0.5 (S)	0.25 (S)	16 (I)	≤1(S)	512 (R)

Abbreviations are as follows: PFT, pulsed-field type; SCC*mec*, staphylococcal cassette chromosome *mec*; CC, clindamycin; DAP, daptomycin; ERY, erythromycin; GM, gentamicin; OXA, oxacillin, LEV, levofloxacin; LNZ, linezolid, PEN, penicillin; Q/D, quinupristin-dalfopristin; SXT, trimethoprim/sulfamethoxazole; TEC, teicoplanin, TET, tetracycline, VAN, vancomycin; S, susceptible; I, intermediate; R, resistant; NS, nonsusceptible.

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Chapter VI

Conclusion

The research for this dissertation used MRSA infection surveillance data collected by MDCH from October 1, 2004 through December 31, 2005 and VRSA data collected during investigations of the first seven cases in the nation. The goal of the first study was to assess the comparability when MRSA infections were categorized as HA or CA by three commonly used classification schemes: healthcare risk factor, infection type, and susceptibility pattern. All three classification methods appeared to be accurate and interchangeable to define MRSA infections, based on the distributions of descriptive variables within the HA and CA categories for each of the three classification schemes. These distributions were consistent with those seen in previously published literature, according to the differing presentations of HA- and CA-MRSA. Individuals with HA-MRSA are generally older, have chronic underlying illnesses, and require more frequent interactions with healthcare facilities, all of which predispose them to more serious and resistant infections. Individuals with CA-MRSA are, in general, otherwise healthy. They are usually not predisposed by age or underlying illness to these infections, but by specific activities and community interactions that place them at an increased risk for acquisition, including but not limited to close contact sports, congregate living and daily activities, and injecting drug use.

The comparative analysis revealed concordance across all three classifications for only 975 (45%) of the cases; 897 (42%) of the cases were consistently defined as HA or CA based on two of the classifications, but not the third. The remaining 279 (13%) cases were missing data that prevented comparison of all three classification methods. These results indicated that the classification of a case as HA or CA was dependent on the method chosen. Each of the three classification methods was inconsistent with the other two, for a number of cases, so it was not possible to identify one method as the most accurate. These noted inconsistencies are somewhat inherent, because each classification scheme defines an MRSA infection using a different characteristic; one considers healthcare interactions of the patient, the second the presentation of infection, and the third the genetic makeup of the pathogen. Each piece of information is important, but when considered in isolation does not present a full picture. Considering the three characteristics together would provide a more complete picture of the MRSA infection; how it was acquired, how it presented, and the specific makeup of the pathogen.

These results suggested that further investigation was needed and analyses should be conducted to search for a more reliable combination of variables that could be used to classify MRSA infection as either HA or CA. Development of a new model was initiated to assess the contribution to the PFGE categorization of the three currently utilized classification schemes of healthcare risk factor, infection type, and susceptibility pattern, plus other variables including age, hospitalization, survival, and preexisting illnesses.

The second study strived to improve the categorization of MRSA infections as healthcare- or community-associated using multivariable statistical methods, in contrast to the previously employed individual classification schemes; healthcare risk factor,

infection type, or susceptibility pattern. This research used a subset of cases defined as HA or CA by PFGE result. A variety of analyses were used including: sensitivity/specificity and predictive value calculations, logistic regression modeling, receiver operating characteristic (ROC) curves, and discriminant analysis.

A number of variables were considered in the development of the new model to more accurately classify MRSA infections as HA or CA, using PFGE result as a gold standard for comparison. Four variables were chosen for the final model, and three of the seven tested variables were eliminated during the analytic selection process. Two of the classification variables, infection type and susceptibility pattern, were selected along with age and hospitalized for inclusion in this new model. The existing differences between the HA and CA groups for each of these four selected variables, along with the high likelihood that the easily obtained data is accurate, makes them strong contributors to the new categorization model. The preexisting illnesses variable and the healthcare risk factor classification variable were most likely eliminated because is it generally difficult to consistently obtain an accurate history on patients. In addition, as the prevalence of CA-MRSA in the community setting continues to increase, an individual with healthcare risk factors could be at greater risk for acquisition of CA-MRSA from their community than risk for acquisition of HA-MRSA from the healthcare settings with which they interact. The survival variable (died during time of MRSA infection) was most likely eliminated because only a small number of all MRSA infections die and often deaths attributed to MRSA are not coded accurately.

The new proposed statistical model identified a combination of basic variables already acknowledged and widely used in differentiating HA- from CA-MRSA infections

that would likely improve on the accuracy of categorizing MRSA infections in and outside of Michigan.

The third study produced the first epidemiologic profile of MRSA infections in the state of Michigan, and demonstrated the discordance between PFGE result reflecting historic HA/CA distribution and healthcare risk factor reflecting current location of acquisition. The surveillance data were collected from a variety of locations including urban, suburban, and rural areas, as well as a number of settings including hospitals, outpatient clinics, long-term care and rehabilitation facilities, correctional facilities, and local health departments. Therefore, it provided a general representation of the entire Michigan population, and allowed for the broad characterization of HA- and CA-MRSA infections in this state. The infections reported through the Michigan MRSA surveillance, with no data missing for critical variables, were categorized as HA or CA by PFGE result if available, or by using the newly developed multivariable statistical model, which predicts the HA/CA classification by considering the type of infection caused by the MRSA organism, the susceptibility pattern of the MRSA organism, the age of the patient, and whether the patient was hospitalized during the MRSA infection.

Results from this investigation highlighted the significant disease burden that the community infections place on the emergency departments and possibly on inpatient units of healthcare facilities, which present an increased likelihood for transmission of CA-MRSA within healthcare settings. Correctional facilities were also revealed as settings with high burden of CA-MRSA infections, which contribute to transmission in the surrounding communities due to a high volume and continual movement of

individuals between these two settings, and transmission of CA-MRSA to and within healthcare facilities as inmates and newly released individuals utilize medical services.

The differences in variable distributions between HA and CA categorizations by the multivariable model Predict result versus healthcare risk factor classification variable were evaluated. The findings identified a group of individuals mostly misclassified due to missing healthcare risk factor data or due to a history of hospitalization in the previous year. Categorization based only on the healthcare risk factor scheme misclassified this specific group of cases. The results from the discordant categorizations indicate that the model appears more consistent and accurate in classifying this group of cases. These results underscored some important messages; individuals in Michigan may be more likely to acquire CA-MRSA from their community than HA-MRSA from brief interactions with healthcare facilities, acquisition of CA-MRSA from interactions with healthcare facilities may be possible, and the new multivariable classification model is an accurate method of classifying HA- and CA-MRSA infections. The information from the new model will help identify where an infection was most likely acquired, as long as the delineation remains between the common settings for HA- and CA-MRSA. This information is pertinent to appropriately target control and prevention efforts.

Reasonable next steps would be to rerun the analyses used in the development of the multivariable classification model with a larger, updated Michigan dataset for validation, and with datasets from other states and possibly a national MRSA dataset to determine whether it is appropriate for areas outside of Michigan. Quickly knowing which type of MRSA is causing an infection provides greater opportunity for the most accurate and targeted educational messages to patients and caregivers for control of

transmission. This is crucial to successful prevention programs aimed at controlling increasing resistance and spread of MRSA.

The fourth and final investigation described the clinical and laboratory characteristics of the first seven patients from whom *vanA*-containing VRSA isolates were recovered. Most of these patients had several characteristics in common including chronic underlying conditions, history of MRSA and VRE infection or colonization, and previous exposure to vancomycin. It is thought that, in all instances, VRE strains likely donated the *vanA* gene to *S. aureus* strains within a polymicrobial biofilm (e.g., wound, nephrostomy tube, or gastrointestinal tract). The transferred *vanA* gene was able to be maintained in the *S. aureus* strains, even without the continued presence of VRE and vancomycin.

Although most of the case-patients exhibited superficial signs of infection at the culture sites, none developed systemic signs or symptoms. This lack of systemic involvement may explain the low attributable morbidity and mortality. All of the VRSA isolates were susceptible to a number of FDA-approved antimicrobial agents. In addition to the variety of antimicrobials used as therapies for the VRSA infections, it is notable that surgical debridement and wound care were important treatment modalities in this case series.

Conjugal transfer of *vanA* plasmid from VRSA strains to *vanA*-negative *S. aureus* strains has been demonstrated. This suggests that, once the initial conjugal transfer of *vanA* from VRE strains to *S. aureus* strains occurs, the spread of *vanA* between *S. aureus* strains might be more likely. Therefore, to ensure implementation of infection control precautions to prevent transmission, clinical microbiology laboratories need to issue

prompt notification of a potential VRSA isolate to infection control personnel. To date, no transmission of VRSA beyond any of the case-patients reported here has been identified.

One of the most prominent, outstanding questions is why five of the seven original cases, plus two more recent additional cases, of VRSA infection occurred in Michigan. This regional emergence likely occurred because of the convergence of several factors, including population characteristics, antimicrobial pressure, and the presence of VRE strains that are more likely to donate *vanA* operon. While each VRSA strain has been distinct, the associated VRE strains from the Michigan patients contain a broad host-range Inc-18 conjugative plasmid that may be more likely to donate *vanA* to other bacterial species, compared with VRE strains from other regions. Future studies will examine the prevalence of these plasmids within enterococcal isolates from Michigan and nationally.

VRSA infections continue to emerge, though as a rare occurrence. Further studies are necessary to investigate the specific characteristics of the *S. aureus* and VRE plasmids isolated from these case-patients. Appropriate antimicrobial prescribing by healthcare providers, adherence to recommended infection control guidelines, and ultimately, the control of both MRSA and VRE are necessary to prevent an increase in emergence of VRSA strains.

In summary, the first portion of this research used Michigan MRSA infection surveillance data to identify classification inconsistencies from three methods that are commonly used to categorize MRSA infections as healthcare- or community-associated. These findings initiated the development of a new multivariable classification model that

was proven to more accurately classify MRSA cases as HA or CA. Findings from the classification of Michigan MRSA infections using the new multivariable model indicate that CA-MRSA places a significant disease burden on healthcare and correctional facilities in the state. The final portion of this research used VRSA case data and emphasized the seriousness of increasing resistance among HA-MRSA organisms, especially in Michigan. The research for this dissertation has shown that the resistant *S. aureus* profile continues to evolve, and control efforts and educational prevention messages must keep up with the changing epidemiology, to effectively combat these adept organisms. To this end, it is crucial that public health efforts to track and characterize these organisms continue.

Appendix. Michigan Department of Community Health Methicillin-Resistant *Staphylococcus aureus* Surveillance Case Report Form.

Michigan Department Of Community Health

MDCH

Methicillin-Resistant *Staphylococcus aureus (MRSA)* Surveillance Case Report Form

Please complete Pages 1 & 2. Fax form to Dawn Sievert at (517) 335-8263.

Reporting Facility _____ **Date** ___/___/___

Type of Facility ☐ Hospital ☐ Long-Term Care Facility ☐ Private Provider ☐ Other _____

Submitter Name _____ **Phone** ( ) ____ - _____

Patient Medical Record No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Patient Name (Last) _____ (First) _____ (MI) _____

Street Address _____ **City** _____

State _____ **Zip code** _____ **County** _____ **Phone** ( ) _____ - _____

Date of Birth ___/___/___

Age _____

Age Units ☐ Days ☐ Months ☐ Years

Gender ☐ Female ☐ Male

Race ☐ White ☐ Black ☐ American Indian/Alaskan Native ☐ Asian ☐ Native Hawaiian/Pacific Islander ☐ Other ☐ Unknown

Ethnicity ☐ Hispanic/Latino ☐ Non-Hispanic/Latino ☐ Unknown

Was patient transferred from another facility? ☐ Yes ☐ No ☐ Unknown

If Yes, list transferring facility's name: _____

If Yes, transferring facility type: ☐ Hospital ☐ Long-Term Care Facility ☐ Private Provider ☐ Other _____

Was the patient hospitalized during current MRSA infection? ☐ Yes ☐ No ☐ Unknown

If Yes: Admission date: ___/___/___ Discharge date: ___/___/___

If Yes, was hospitalization initially due to current MRSA infection? ☐ Yes ☐ No ☐ Unknown

Patient Outcome: ☐ Survived ☐ Died ☐ Unknown If Died: Date of death: ___/___/___

If Died, was the current MRSA infection contributory/causal? ☐ Yes ☐ No ☐ Unknown

Patient underlying medical conditions or prior illnesses (check all that apply):

☐ None	☐ Alcohol Abuse	☐ Asthma	☐ Chickenpox	☐ Chronic Renal Insufficiency
☐ Current Smoker	☐ CVD/CAD	☐ Diabetes Mellitus	☐ Dialysis (HD/PD)	☐ Eczema
☐ Emphysema/COPD/Bronchopulmonary Dysplasia		☐ Folliculitis	☐ Heart Failure/CHF	☐ HIV/AIDS
☐ Immunosuppressive Therapy	☐ Injection Drug Use	☐ Liver Disease	☐ Malignancy-Hematologic	☐ Malignancy-Solid Organ
☐ Psoriasis	☐ Shingles	☐ Shunt (ie. VP)	☐ Wound/Burn	

☐ Other (specify) _____ ☐ Unknown

Please include a copy of the Laboratory Susceptibility Test Results with this form.
Contact Dawn Sievert at (517) 335-9001 if isolates are available for PFGE testing.

Page 1 of 2 ***continued***

MRSA Surveillance Case Report Form

Patient Med. Rec. No._____

Culture date for MRSA specimen: ___/___/___

Culture site from which MRSA organism was isolated:

☐ Blood ☐ CSF ☐ Pleural Fluid ☐ Peritoneal Fluid ☐ Joint ☐ Bone ☐ Surgical Specimen

☐ Post-Op Wound ☐ Skin (swab/aspirate) ☐ Sputum/Trach ☐ Nares ☐ Device/Catheter ☐ Urine

☐ Ear (drainage/aspirate) ☐ Eye ☐ Other (specify) _____

If Skin culture site, specify body site: ☐ Foot ☐ Leg ☐ Hand ☐ Arm ☐ Head ☐ Neck

☐ Chest ☐ Armpit ☐ Trunk ☐ Groin ☐ Buttocks

Type of infection associated with current MRSA culture (check all that apply):

☐ None ☐ Bacteremia ☐ Bursitis ☐ Meningitis ☐ Osteomyelitis

☐ Otitis (media or external) ☐ Pneumonia ☐ Septic Arthritis ☐ Skin Infection: Abscess ☐ Skin Infection: Cellulitis

☐ Skin Infection: Folliculitis ☐ Skin Infection: Impetigo ☐ Surgical Site Infection ☐ Wound Infection

☐ Other (specify): _____ ☐ Unknown

Antibiotics prescribed to patient for the current MRSA infection? ☐ Yes ☐ No ☐ Unknown

If Yes, specify antibiotic 1: _____ Total # days prescribed: _____

If Yes, specify antibiotic 2: _____ Total # days prescribed: _____

If Yes, specify antibiotic 3: _____ Total # days prescribed: _____

If Yes, specify antibiotic 4: _____ Total # days prescribed: _____

Does the patient have ANY of the following risk factors (check all that apply):

☐ History of known MRSA infection or colonization?
☐ Contact to person with MRSA infection/colonization within previous year?
☐ Hospitalized >48 hours prior to current MRSA infection?
☐ In ICU >48 hours prior to current MRSA infection?
☐ Hospitalized in year prior to current MRSA infection?
☐ Surgery in year prior to current MRSA infection?
☐ Dialysis in year prior to current MRSA infection?
☐ Percutaneous device or indwelling catheter (i.e. IV, PICC, foley, tracheostomy) in year prior to current MRSA infection?
☐ Reside in long-term care/ nursing home/ rehabilitation facility in year prior to current MRSA infection?
☐ Attend a daycare (child or adult) in year prior to current MRSA infection?
☐ Live in close congregate setting (i.e.: jail/prison, group home, dormitory) in year prior to current MRSA infection?
☐ Work in health care field?
☐ Close contact to a health care worker?
☐ Use a hot tub/sauna/steam bath in year prior to current MRSA infection?
☐ Use a public pool/water park in year prior to current MRSA infection?
☐ Use a public shower/bath in year prior to current MRSA infection?
☐ Share towel with someone after swimming/bathing in year prior to current MRSA infection?
☐ Share health/beauty aids (i.e.: soap, razor, deodorant, lotion, lubricant) in year prior to current MRSA infection?
☐ Participate in any sports in year prior to current MRSA infection?
☐ Share equipment/clothing/uniform just prior to current MRSA infection?
☐ Have existing skin abrasions just prior to current MRSA infection?
☐ Have any pets?
☐ Use of antibiotics in 6 months prior to current MRSA infection?

If Yes, specify antibiotic 1: _____ Total # days prescribed: _____

If Yes, specify antibiotic 2: _____ Total # days prescribed: _____

If Yes, specify antibiotic 3: _____ Total # days prescribed: _____

If Yes, specify antibiotic 4: _____ Total # days prescribed: _____

☐ Close contact to a person known to have any of the above risk factors within previous year?

Please fax to Dawn at 517.335.8263