AN ASSESSMENT OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* OUTSIDE HOSPITAL SETTINGS IN ALLEGHENY COUNTY, PENNSYLVANIA

by

Jennifer Lynn Lucado

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This thesis was presented

by

Jennifer Lynn Lucado

It was defended on

April 11, 2008

and approved by

Stewart Anderson, Ph.D., Professor, Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh

Rodger L. Beatty, Ph.D., L.S.W., Assistant Professor, Department of Infectious Diseases and Microbiology, Graduate School of Public Health, University of Pittsburgh

Thesis Director: Lawrence A. Kingsley, Dr. P.H., Associate Professor, Department of Infectious Diseases and Microbiology, Graduate School of Public Health, University of Pittsburgh

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is an infectious disease that has been a cause of nosocomial infections since the 1960s, but has more recently become an emergent disease in community settings. MRSA infections that develop outside hospitals have been associated with risk factors such as young age, recent antibiotic use, recent contact with health care, and dermatological conditions. To provide descriptive epidemiological data and evaluate potential risk factors, we undertook a case-control study of Allegheny County residents with laboratory-confirmed MRSA and methicillin-sensitive *S. aureus* (MSSA) cultures from January through August of 2007. A random sample of each group was contacted and interviewed using a standardized questionnaire. Comparing 54 MRSA culture-positive residents to 50 MSSA culture-positive residents, we found that having a reported self history of MRSA ($p<.001$), having a household member or self recently having been in the hospital ($p=.041$), and having a household member or self recently having been in a community living setting ($p=.032$) were significant risks of having a positive MRSA culture. These findings have public health significance because as a greater number of people become infected or colonized by MRSA, the reservoir in the community will continue to grow, resulting in a greater number of infections and increased morbidity and mortality from the disease.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

I want to thank Dr. Kingsley for his guidance through the practicum and thesis process and Dr. Beatty and Dr. Anderson for their helpful feedback on my thesis. I would also like to thank the Allegheny County Health Department for their support that allowed me to complete this investigation, and Dr. LuAnn Brink for all of her advice along the way. Thank you to Dr. Day and Mei Han of the University of Pittsburgh Graduate School of Public Health Biostatistics Department for the expert help in interpreting the relatedness of the potential risk factors. Also, to my parents, my roommate, Gina, and other friends and relatives, thank you for tolerating the number of times the words “MRSA” and “thesis” came up in our conversations over the past six months.

1.0 CHARACTERIZATION OF *STAPHYLOCOCCUS AUREUS* EPIDEMIOLOGY

Staphylococcus aureus bacteria have a long-established history as a cause of human disease around the world. Before the advent of antibiotic use, invasive *S. aureus* infections were almost always fatal (1). The introduction of penicillin greatly improved prognosis for these serious cases of infection; however, resistant strains of bacteria appeared within a few years, due to bacterial production of β-lactamases. In 1960, methicillin was introduced as an alternative treatment for penicillin-resistant bacteria, but a mere six months after its introduction, a hospital in the United Kingdom reported methicillin-resistant *S. aureus* (MRSA). Since then, MRSA has become a problem worldwide, causing much concern in the 1980s when it became the cause of many nosocomial infections. In 1993, the epidemiology of MRSA became more complex when a genetically novel strain of community-associated MRSA (CA-MRSA) was reported. Previously, MRSA was only seen in people who had frequent contact with health care facilities. Residents of chronic-care facilities and people who had long or repeated hospital stays were the most likely to develop the infection (2). However, this first strain of CA-MRSA was discovered in indigenous populations living in Western Australia who had no previous contact with the health care system, a pattern of risk that is becoming increasing common in the United States today (3).

1.1 BACTERIAL INFORMATION

1.1.1 Genetics

S. aureus, a member of the Micrococcaceae family, has a circular chromosome about 2800 bp in length that contains prophages, plasmids, and transposons. Genes controlling virulence and resistance to antibiotics are found on both the chromosome and extrachromosomal elements. These genes can be transferred between all types of gram-positive bacteria through extrachromosomal elements called plasmids (4).

1.1.2 Methicillin resistance genes

Methicillin resistance in *S. aureus* is due to the presence of the *mecA* gene. The 2.1-kb *mecA* gene encodes the 78-kDa penicillin-binding protein (PBP) 2a (or PBP2'). PBPs are membrane-bound enzymes that catalyze the transpeptide reaction that is necessary for the cross-linkage of the peptidoglycan chains that are a major component of the staphylococcal cell wall (5). β-lactam antibiotics normally bind to PBPs in the cell wall, causing a disruption of the synthesis of peptidoglycan layer necessary for cell growth and resulting in cell death. However, the PBP2' protein has a low affinity for β-lactam antibiotics such as methicillin, so even in the presence of these antibiotics, peptidoglycan synthesis and normal cell wall growth will continue uninterrupted (1).

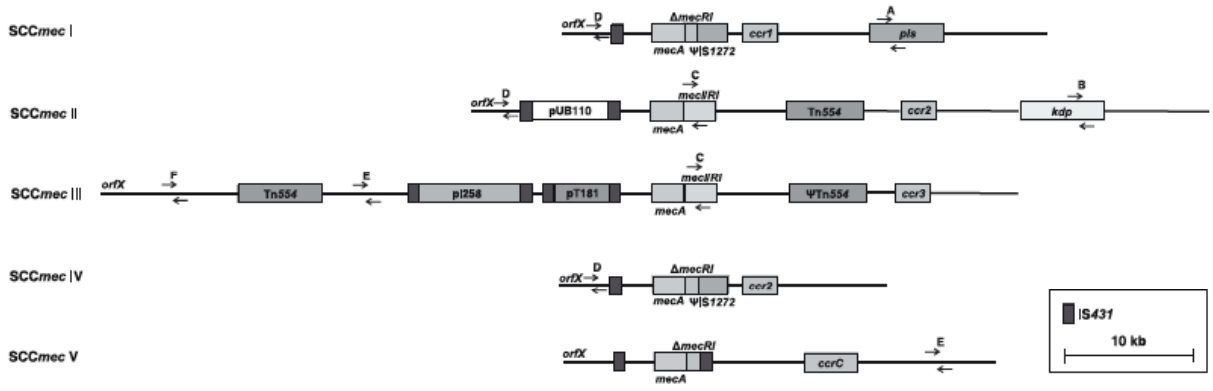


Figure 1. A schematic arrangement of SCC*mec* types I - V. From Deurenberg et al. (6).

The *mecA* gene is located on a mobile genetic element, known as the Staphylococcal Cassette Chromosome *mec* (SCC*mec*). As shown in Figure 1, there are currently five main types of SCC*mec* that have been characterized, ranging in size from 20.9 to 66.9 kb. The three shorter types, I, IV, and V, only encode resistance to β-lactam antibiotics. Types II and III, however, encode additional types of antibiotic resistance through genes contained on integrated plasmids (pUB110, pI258, and pT181) and a transposon (Tn*554*). Plasmid pUB110 provides resistance to kanamycin, tobramycin, and bleomycin; pI258 provides resistance to penicillins and heavy metals; and pT181 provides resistance to tetracycline. Transposon Tn*554* carries the *ermA* gene, which is responsible for the inducible macrolide, lincosamide, and streptogramin resistance (6).

SCC*mec* also contains genes that regulate the *mecA* transcription and insertion sequences that allow it to integrate into the staphylococcal chromosome at a specific site within an open reading frame. The regulation genes ensure that *mecA* is only transcribed in the presence of β-lactam antibiotics; in their absence, the trans-membrane β-lactam-sensing signal-transducer MecRI waits to sense the presence of the antibiotics. When β-lactam antibiotics are present,

MecRI is cleaved and the metallo-protease domain becomes activated, which, in turn, cleaves the MecI bound to *mecA* and allows *mecA* transcription (6).

1.1.3 Panton-Valentine leukocidin

Another element commonly found in MRSA is the Panton-Valentine leukocidin (PVL), a leukocytolytic toxin that has been associated with necrotic skin lesions and community-acquired pneumonia. PVL is a member of the synergohymenotropic toxin family. This is a family that also includes γ-hemolysin, a toxin produced by over 99% of *S. aureus* clinical strains. Members of this family damage the membranes of host defense cells and erythrocytes via the synergistic effects of 2 non-associated classes of secreted proteins, designated class S and F; for PVL, these proteins are LukS-PV and LukF-PV. LukS-PV and LukF-PV can cause damage by working with one another or by working with the γ-hemolysin S proteins (HlgA and HlgC) and F protein (HlgB), making 6 possible active pairs. Any protein pair that includes one PVL protein has been shown to have necrotic effect on tissue, whereas, a pair consisting of only γ-hemolysin proteins will only have inflammatory effects (7).

1.1.4 Lab methods for detection

In order to positively identify the presence of *S. aureus*, laboratories must isolate a pure culture of the bacteria, looking for distinctively colored, circular, raised growths on the agar plate. Colonial color may range from grey to yellow to orange, depending upon the amount of carotenoids present. Under the microscope, the bacteria have the appearance of non-motile, gram-positive clustered spheres. Most strains of *S. aureus* are able to grow on 10% NaCl agar

and will aerobically produce acid from D-Mannitol and D-Trehalose, unlike their close relative *S. epidermis*, the other type of staphylococcus commonly found in humans. *Staphylococcus aureus* will also test positive for coagulase and clumping factor (8). To test for methicillin resistance, the Clinical and Laboratory Standard Institute (CLSI) recommends several different methods, including broth and agar dilution, disk diffusion, and agar screen methods. All tests should be carried out at a maximum incubation temperature of 35°C and final readings should take place after 24 full hours of incubation. Specific directives for these recommendations can be found in the CLSI document M100-S15 (1).

1.2 CLINICAL MANIFESTATIONS

Staphylococcus aureus is a major cause of skin, soft tissue, eye, respiratory, bone, joint and endovascular disorders, ranging in severity from localized and easily treatable to invasive and life threatening (4). MRSA causes the same types of infections as methicillin-sensitive strains of *S. aureus* (MSSA). Extremely common clinical manifestations of MSSA and MRSA infections are skin and soft tissue infections. Soft tissue abscesses, infections at wound sites, impetigo, cellulitis, and folliculitis are the most common outcomes of skin infection (9). In the case of MRSA, abscesses are common; patients with abscesses frequently describe the start of infection as a "spider bite." This initial pustule is usually small in size and surrounded by cellulitis, but the infection often leads to abscess formation with progressive cellulitis, marked by tissue necrosis (10).

In the eyes, most infections manifest as preseptal cellulitis and/or a lid abscess followed by conjunctivitis. However, there are more serious cases involving corneal ulcers,

endophthalmitis, orbital cellulitis, and blebitis that have been observed, all of which are serious threats to sight (11). The bacteria are also known to cause otitis media, or middle ear infection. In one case study, a child with a history of otitis media and bilateral tube placement was found to have MRSA as the causative agent of a severe infection (12).

Most skin infections are localized and are a minimal threat to health. However, infections can become invasive. Invasive infections can result in bacteremia, endocarditis, acute osteomyelitis, and septic shock (13). In some cases of *S. aureus* bacteremia, especially in elderly patients, vertebral osteomyelitis may occur as a complication, resulting from staphylococci exiting the bloodstream and lodging themselves in previously damaged vertebra. *S. aureus* is also the second most common cause of prosthetic joint infections, such as those of the hip or knee (14), and can cause septic arthritis (15). MSSA and MRSA are also known to cause pneumonia, especially with ventilator use (16); MRSA stains containing PVL genes have been shown to cause necrotizing pneumonia (17).

1.3 TREATMENTS AVAILABLE

Treatments available for MRSA infection vary depending upon the site of infection and the antibiotic sensitivity of the particular strain. In general, the incision and drainage of an abscess or removal of an infected medical device is the most important first step to treatment. Antibiotic selection, however, is also integral to successful treatment. Recommendations for antibiotic selection vary, which is undoubtedly due, in part, to changes in additional drug resistances that have developed over time. According to MRSA researcher B.A. Cuhna, research has shown that *in vitro* antibiotic susceptibility is not always predictive of *in vivo* susceptibility

of a particular strain. He asserts that trimethoprim-sulfamethoxazole (TMP-SMX) has shown variable results against MRSA, and that rifampin is known to be effective in treating staphylococcal infections, but has yet to be demonstrated effective against MRSA. He recommends using five antimicrobial agents with consistently high demonstrated degrees of effectiveness *in vivo* against MRSA: quinupristin/dalfopristin, minocycline, daptomycin, linezolid, and vancomycin. All of these are available in intravenous form, but minocyline and linezolid are both available in oral form, allowing patients to medicate at home at a low cost compared to the intravenous options (14). However, serious, invasive infections are most often treated with intravenous vancomycin (18). Another source recommends TMP-SMX or doxycyline as first-line agents and clindamycin and linezolid as second-line agents, noting that the second-line agents have high levels of inducible resistance (9). TMP-SMX is commonly prescribed for treatment in outpatient settings, often in combination with rifampin, to minimize the likelihood of the development of resistance, and an estimated 95% CA-MRSA isolates are susceptible to the agent (19). As with many other antibiotics used for the treatment of MRSA, it seems that TMP-SMX resistance is also becoming more common, especially in hospitals. In 2004, it was estimated that 40% to 50% of MRSA isolates in Canadian hospitals were resistant to TMP-SMX treatment (20).

1.4 HUMAN COLONIZATION PATTERNS

1.4.1 Colonization and the host response

Staphylococcus aureus has long been known to colonize the human body. Colonization has been defined in a number of ways, but most definitions have wording similar to the following: the presence of a microorganism not part of the normal flora of the host that is multiplying. Colonization may or may not trigger a microbe-specific immune response in the host. If a specific immune response occurs, the microbe could be eliminated; if not, disease may ensue and damage may occur. As a result of this range of outcomes, colonization is observed in individuals for variable lengths of time (21). In the first half of the twentieth century, researchers found that the anterior nares was the most consistent site of *S. aureus* colonization (22). However, cutaneous surfaces, conjunctiva, the intestinal tract, and the throat have since been found to be very common sites of colonization (23-25).

1.4.2 Endogenous infection

The most common threat evaluated regarding colonization is endogenous infection. In a hospital setting, it has been found that people who are nasal carriers are more likely to become infected with endogenous *S. aureus*. Beginning in the late 1950s, researchers have also examined the link between *S. aureus* nasal carriage and surgical wound infections. Comparing the rate of *S. aureus* infection of carriers to that of non-carriers, the risk ratios calculated in these studies range from 0.7 to 12.1, most likely due to differences in study populations (26). Some relatively recent studies have focused on nasal carriage and bacteremia. In one prospective study

conducted in Germany, 1278 patients were found to have nasal colonization with *S. aureus* upon hospital entry; of these patients, 14 (1.1%) subsequently developed *S. aureus*-caused bacteremia. In 12 of these 14 patients (86%), the bacterial strain found in the blood was a genetic match to the bacteria previously found in the nose (27). So, while the risk of developing bacteremia is very small, the chances that bacteremia is caused by the same strain of bacteria that a patient was already colonized with is very great. Another prospective study in the Netherlands found nosocomial *S. aureus* bacteremia to be three times more frequent in *S. aureus* carriers than in non-carriers, with 80% of carrier infections being endogenous. However, the rate of *S. aureus* bacteremia-related deaths was significantly higher in non-carriers than in carriers. This suggests that either the endogenous strains were less virulent than the exogenous strains or that carriers could be immunologically adapted to the *S. aureus* strain they carry, providing them with more adequate immune responses than non-carriers (28).

1.4.3 Use of mupirocin for prevention of nasal colonization

If nasal carriage of *S. aureus* can lead to infection, it follows that the elimination of carriage could lead to reduced rates of infection; as a result, many studies have been performed on the effects of local antibiotics or disinfectants. Mupirocin (Bactroban) is one topical antibiotic that has shown promise in eliminating nasal carriage effectively in healthy people (26). In a randomized, double-blind placebo-controlled study (29), researchers founds that application to the nose twice daily for 5 days eliminated nasal carriage in 91% of stable nasal carriers, as illustrated in Figure 2. Four weeks after the completion of treatment, 87% of the treatment group continued to be free of nasal carriage (compared to elimination in 7% of the placebo group). At 6 months post-treatment, the carriage rates in treatment and control groups were 48% and 72%,

respectively (30). At 12 months post-treatment, the carriage rates in treatment and control groups were 53% and 76%, respectively. For those who received treatment, 36% were colonized with a new strain of *S. aureus* at 12 months and 34% were recolonized by the strain they originally carried. These studies also suggest that the hands are a primary site of *S. aureus* colonization because investigators found that 87% of *S. aureus* isolates from the participants' hands were genetic matches of the isolates that had originally colonized the nose.

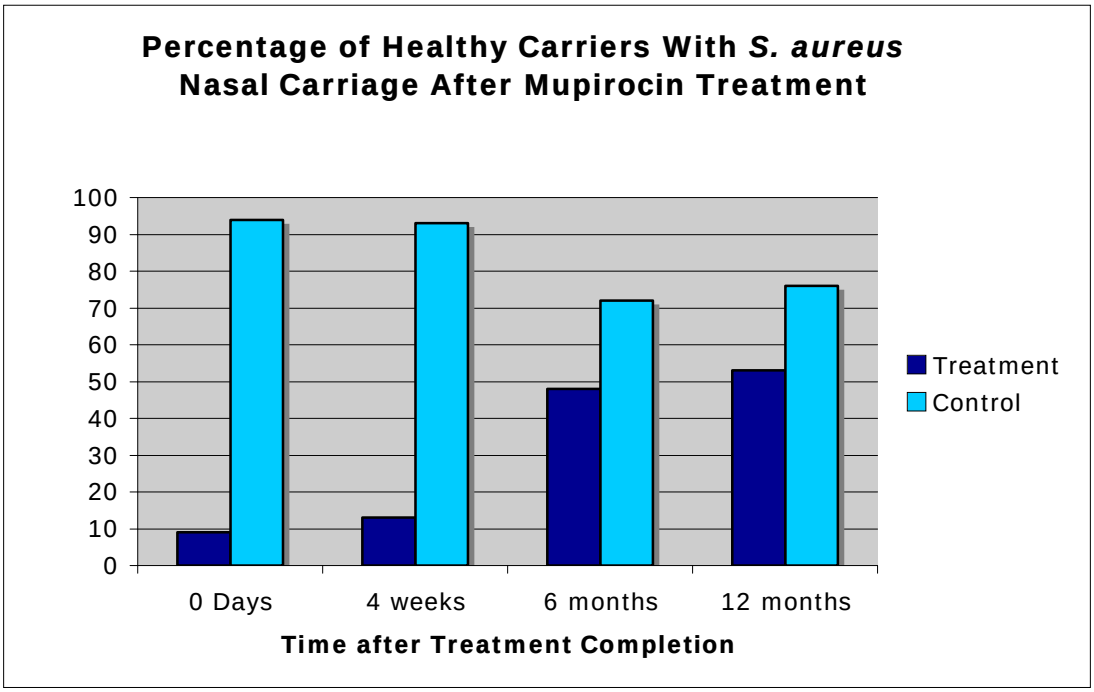


Figure 2. Nasal *S. aureus* colonization in healthy carriers after mupirocin treatment. Adapted from Doebbeling et al. (29, 30).

According to studies of patients with compromised immunity, mupirocin treatment eliminates *S. aureus* carriage with lower efficacy. In one study of patients undergoing hemodialysis (31), the rate of carriage was reduced from 90% before treatment to 33% directly following treatment. At 4 months post-treatment, the nasal carriage rate rose to 66%. These

results suggest that elimination is less likely and that hemodialysis patients either have a greater number of alternate sites of colonization on their bodies or they are more likely to be recolonized from external sources than healthy people are.

1.4.4 Person to person transmission

Little is known about the means of spread for *S. aureus* colonization. Colonized people are the most obvious reservoir from which the bacteria may be acquired. One study found that nasal and/or intestinal colonization by *S. aureus* was correlated with an increased frequency of positive skin cultures on the patient, the surrounding environment, and the hands of patient care staff. Patients with nasal or intestinal colonization were more likely than non-colonized people to have diarrhea, infection, and increased lengths of stay, which are all factors that could increase the likelihood of spread within a hospital (24). Other studies have examined MRSA carriage in dialysis patients, health care workers and their families. One study in Taiwan found a significantly higher rate of carriage in the immediate family of health care workers than in the immediate family of dialysis patients (32). This speaks to the importance of hand washing that is often emphasized for preventing the spread of these bacteria, especially for health care workers after caring for each patient and before leaving work for the day.

2.0 A SHORT HISTORY OF MRSA

In 1960, a mere six months after the introduction of methicillin as treatment for *S. aureus*, a hospital in southern England reported finding several isolates of MRSA (33). Initially, this appeared to be a unique occurrence and microbiologists were optimistic of the continued effectiveness of methicillin; however, by 1967, MRSA had also been reported in Switzerland, France, Denmark, Australia, and India. After the initial appearance of MRSA throughout the continent, Europe saw a rise and then fall, for unknown reasons, in the prevalence of MRSA through the early 1980s. In the 1980s, however, concerns about MRSA rose again when multi-drug resistant MRSA was reported in Ireland, the United Kingdom, and the US; one particular strain was suspected to have spread from an outbreak in Australia to cause an outbreak the United Kingdom (3).

For many years, the only cases of MRSA found in the community were in people who had frequent contact with health care facilities (3). However, in 1993, a strain of MRSA genetically distinct from the known hospital strains was discovered in indigenous people living in Western Australia who had no previous contact with the health care system (34). In the United States, an increasing number of CA-MRSA cases were noted in the late 1990s. This caused a scare because people who were otherwise healthy and had with little contact with the health care system were hospitalized or died from MRSA. In 1998, a group of Chicago researchers described 26 children hospitalized for community-associated MRSA who lacked

traditional health care-associated risk factors (35). Since then, the number of MRSA cases reported in the community has increased greatly. Clusters of MRSA infection have been investigated among children, newborns, athletes, military personnel, prisoners, and tattoo recipients (36-41). Despite these investigations, the public health community still lacks a clear epidemiological picture of the disease.

3.0 EPIDEMIOLOGY OF MRSA

3.1 DEFINITIONS OF HA-MRSA VERSUS CA-MRSA

One of the greatest challenges in MRSA investigations is simply differentiating between hospital and community cases of the infection. One variation in wording is the use of "hospital associated," "hospital acquired," or "HA" versus using the word "nosocomial." Community cases may be referred to as "community associated," "community acquired," "community onset," "community derived," or "CA." For the purposes of their Active Bacterial Core Surveillance Program, the CDC has defined a community-associated MRSA (CA-MRSA) case as a patient with a MRSA infection and no history of the following: surgery, hospitalization, residence in a long-term care facility, or dialysis within one year prior to infection; presence of a percutaneous device or indwelling catheter; hospitalization >48 hours before the culture; or history of previous MRSA infection or colonization (42). Conversely, a case of HA-MRSA can be defined as any MRSA infection that does not qualify as CA-MRSA.

Many studies have used the term, "community acquired" to classify the cases of infection, with the main criteria for selection being the development of MRSA infection while being outside of the hospital or developing it within 48 hours of hospitalization. The term implies that the bacteria causing the infection were acquired in the community, outside of hospital settings. The problem with this classification, however, is that people may develop a

MRSA infection outside of the hospital setting, but may have acquired the bacteria during a recent hospital stay. These patients would not be differentiated from patients lacking a history of hospitalization because risk factors were not assessed. Thus, HA-MRSA cases would be included in the counts of community-acquired MRSA cases. CA-MRSA can also become ambiguous when it is defined by genetic or endotoxin presence. This is a problem because some strains of MRSA that have genetic characteristics traditionally associated with CA-MRSA are presenting in hospitals, which creates a very fine line between genetically-defined HA-MRSA and CA-MRSA. In this thesis, the only categories referred to will be CA-MRSA and HA-MRSA. CA-MRSA will always refer to "community-associated MRSA" and HA-MRSA will refer to "hospital-associated MRSA," taking into account the time and place of infection development, rather than the genetic makeup of the bacteria. For the most part, the characterization of CA-MRSA does not exclude patients with health care contact risk factors that would cause them to be excluded by the CDC definition.

3.2 PREVALENCE OF NASAL CARRIAGE

As previously stated, *S. aureus* is a very common colonizer of humans. As part of the CDC's comprehensive National Health and Nutrition Examination Survey 2001-2002, nasal samples were obtained from a representative sample of the United States (US) population and tested for the presence of *S. aureus* and MRSA (22). From these results, it was estimated that 32.4% (95% confidence interval [CI], 30.7%-34.1%) of the US population is nasally colonized with *S. aureus* and 0.8% (95% CI, 0.4%-1.4%) is nasally colonized with MRSA. The greatest prevalence of *S. aureus* colonization was observed in children aged 6 to 11. MRSA colonization

was associated with the age of 60 years or greater and being female, but was not associated with recent health care exposure. Other than this nasal data, not much is known about the prevalence of colonization for other areas of the body. As previously explained, some colonization studies show that people may be colonized in other common external locations, such as the throat (25) or skin (12), without concurrent colonization in the nose. Thus, the prevalence estimates based solely on nasal colonization may be an underestimate of population prevalence.

3.3 COMPARISON OF HA-MRSA VERSUS CA-MRSA EPIDEMIOLOGY

3.3.1 Hospital-Associated MRSA epidemiology

3.3.1.1 Trends

3.3.1.1.1 Geographic variability

The prevalence of HA-MRSA varies greatly by geography. The European Antimicrobial Resistance Surveillance System (EARSS) is responsible for monitoring the prevalence of MRSA and changes over time in most European countries. From 1999 through 2002, they collected 50,759 nosocomial isolates from 495 hospitals in 26 countries. Researchers found large variations in the incidence of MRSA between countries and sometimes between hospitals within a country. In some northern countries, such as Sweden and Denmark, the prevalence was less than 1%; in some southern countries, such as Greece and Italy, and the United Kingdom (UK), the prevalence was upwards of 40%. Variation within countries was greatest in countries with prevalence between 5% and 20%.

Figure 3. Geographic variation in proportions of MRSA detected by EARSS (1999 - 2002). From Tiemersma et al. (43).

3.3.1.1.2 Rise in prevalence of MRSA isolates

EARSS also observed that some countries had statistically significant changes in the percentage of cases during the study period. The UK saw the greatest percentage increase, from 30.5% in 1999 to 44.5% in 2002. Slovenia was the only country to show a significant decrease, declining from 22.3% to 14.7% (43). In the US and some Asian countries, an increase in HA-MRSA has also been observed. One study based in a large Taiwan university hospital found the prevalence of MRSA isolates increased from 26.7% of nosocomial infections in 1990 to 77% in 2001; as an incidence rate, 8.9 per 100,000 discharges from the hospital in 1990 had HA-MRSA, but 32.6 per 100,00 had it in 2000 (44).

3.3.1.1.3 Estimation for incidence of invasive MRSA

Recently, an attempt was made to characterize life-threatening MRSA cases in the US. In 2007, information was released from the Active Bacterial Core surveillance system on the incidence of invasive HA-MRSA infections in several geographic areas. Researchers found that of all invasive cases of MRSA in these cities, 85% were health care-associated; specifically, 26.6% developed in the hospital and 58.4% developed outside of the hospital. As with the EARSS data, incidence variation by geography was also observed in this study. HA-MRSA that developed while in the hospital, for example, ranged from 6.1 per 100,000 persons for Ramsey County, Minnesota to 19.7 per 100,000 persons for Baltimore City, Maryland (13).

3.3.1.1.4 Threat to intensive care unit patients

MRSA infections are a common problem for patients in intensive care units (ICUs). Patients in the ICU are those with the most life threatening conditions. Because of this stress on the body, ICU patients are at great risk of HA-MRSA infection because a combination of lowered immune response and the utilization of many medical devices, such as catheters and mechanical ventilation, that can serve as additional sites of colonization and entryways into the body. In the ICU, it is estimated that 20% of patients are colonized or will become colonized with MRSA during their stay (45). The percentage of *S. aureus* isolates that were MRSA in ICUs from 1998 to 2002 was 48.5%, and in the year 2003, the proportion of MRSA isolates in ICUs increased by 11% to 59.5% (46). Historically, it is estimated that the percentage of MRSA isolates in ICU patients has increased from 29% in 1989 to over 60% in 2002 (45). In the general hospital patient population, MRSA rates are likewise high. According to one report by the National Nosocomial Infections Surveillance System (NNISS), from January 1998 through

June 2003, 42% of *S. aureus* isolates in non-ICU patients were MRSA (47). However, the rates are still slightly higher in ICUs.

3.3.1.2 Common strains of HA-MRSA detected

In the US, the most MRSA strains most commonly found to be associated with hospitals include pulsed field gel electrophoresis (PFGE) patterns USA100, USA200, and USA800. The USA100 strain is the most prevalent strain by far; it is estimated that 43% of MRSA can be typed as USA100 (48). The prevalence of other strains is shown below in Figure 4.

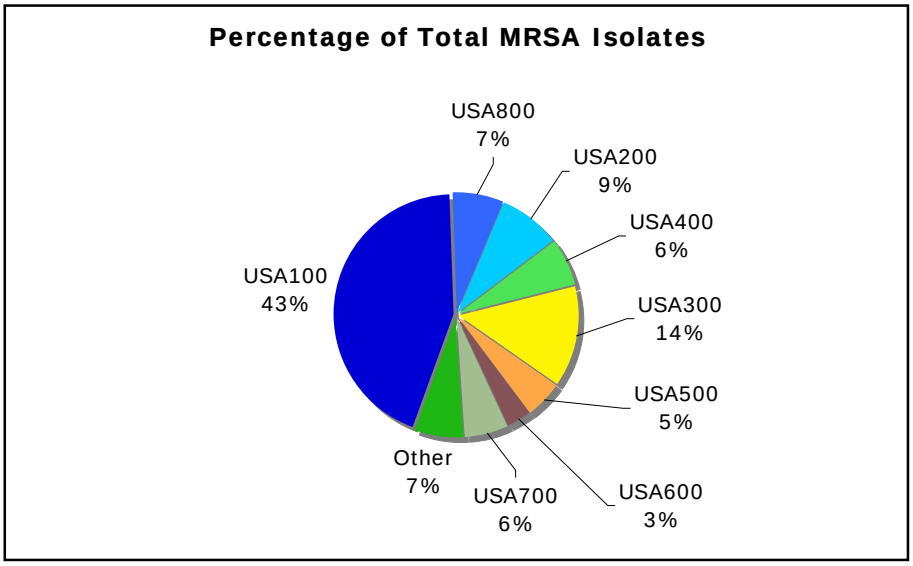


Figure 4. MRSA strains by percentage of prevalence in the US. Adapted from McDougal et al. (48).

In HA-MRSA strains, genetic elements vary by isolate. Hospital associated isolates have been found to most commonly carry SCC*mec* types I, II, and III (49). SCC*mec* types II and III are both larger elements that have the ability to provide resistance to additional antibiotic types, so HA-MRSA has commonly been associated with multi-drug resistance (50). The prevailing

type of SCC*mec* found in HA-MRSA isolates is II, but prevalence varies geographically. At a military hospital in San Diego, 94% of HA-MRSA isolates contained SCC*mec* type II (51). In a Minnesota study, 81% of HA-MRSA isolated carried SCC*mec* type II (50). In San Francisco, however, among HA-MRSA strains in hospitals, about 48% carried type II. The remaining 52% carried SCC*mec* type IV, which is commonly found in CA-MRSA, suggesting that a reservoir of CA-MRSA was well established in the community and has the ability to move into the hospital setting. Interestingly, in San Francisco long-term care facilities, 81.6% of MRSA strains carried SCC*mec* type II, similar to the Minnesota figures (52).

3.3.1.3 Common clinical manifestations of HA-MRSA

HA-MRSA is known to cause a wide range of infections and is more likely than CA-MRSA to cause invasive infections. In one study, investigators collected data on HA-MRSA infections from 1990 to 2004 and found that MRSA was responsible for the infection of sites listed with the frequencies shown in Table 1 (51). Sites covered in the "other" category included samples from body fluids, bone, and heart valves, indicating invasive infection types. For HA-MRSA, skin and soft tissue infections are often at surgical site incisions (SSIs). In fact, it was estimated by a 2003 study that 29% of culture positive SSIs were caused by MRSA (53). Other major infection types that are more common to HA-MRSA than CA-MRSA include respiratory and urinary infections. As shown in Table 1, Crum and her colleagues found in their research that 19% of MRSA infections were in the lungs (sputum) and 12.3% were in the urine. However, that study was based out of a military hospital, so the results might not be typical of a hospital serving the general public. Other studies have found higher proportions of these infection types. In a San Francisco study, estimates for the percentage of MRSA infections in hospitals that were respiratory and urinary were 31.6% and 17.6%, respectively (52). The

proportion of MRSA infections affecting the urinary tract might be more common in long term care facilities; in San Francisco, 29.6% of MRSA cases were urinary (52). For respiratory infections—pneumonia specifically—MRSA has been estimated to be responsible for 22.9% of hospital-associated pneumonia cases. Ventilator-associated pneumonia (VAP) has always been a threat to ICU patients and now MRSA is increasingly the cause of VAP. One study in press found that 14.6% of VAP was caused by MRSA (54).

Table 1. Frequency of distribution of HA-MRSA infection by site. Adapted from Crum et al. (51).

Site of Infection	HA-MRSA Cases n=457
Soft tissue/abscess	218 (47.7%)
Sputum	87 (19.0%)
Blood	71 (15.5%)
Urine	56 (12.3%)
Catheter/foreign device	52 (11.4%)
Multiple simultaneous sites of infection	45 (9.8%)
Other	19 (4.2%)
Ear/nose/sinus/throat	12 (2.7%)
Cerebrospinal fluid	3 (0.7%)
Not documented	1 (0.2%)

3.3.1.4 Risk factors for HA-MRSA

Some pre-existing conditions have been found to increase the likelihood of HA-MRSA infection. Chronic medical illnesses are one example. Patients undergoing hemodialysis treatment and patients with HIV infection are two groups at higher risk for infections of all

kinds, including MRSA (45). Many patients undergoing hemodialysis have chronic renal failure, a condition associated with reduced chemotaxis and phagocytosis that results in an impaired immune system. Combine that effect with higher observed rates of skin and nasal colonization by *S. aureus* in dialysis patients and the repeated penetration of the skin barrier required for treatments, and the increased infection rate seems to be a likely outcome (31). The biggest risk for developing infection, though, is carriage of the bacteria. In Sista's review of *S. aureus* infections in ICU patients, a summary of risk factors for carriage was reported (Figure 5) (45). One study looking at colonization found that 44% of ICU patients who were colonized with MRSA went on to develop MRSA infections. However, they also found that 40% of infected patients were colonized and infected in the same day, which could explain why colonization has not always been found to precede infection (55).

Box 1. Risk factors for methicillin-resistant *Staphylococcus aureus* carriage

Previous colonization (nasal/cutaneous)
Age > 60 years
Exposure to a patient known to be colonized or infected with MRSA
Host factors
- History of stay in an ICU during the last 5 years
- History of surgery during the last 5 years
- Prolonged hospital stay (21 days or longer)
- Intravenous drug use
- Residence in a skilled nursing facility
- Presence of open skin lesions

Chronic medical illness
- Diabetes mellitus Type I
- Patients undergoing hemodialysis

Impaired immune function
- AIDS
- Quantitative defect in leukocyte function
- Qualitative defect in leukocyte function (eg, Chediak-Higashi syndrome, chronic granulomatous disease, Job's syndrome)

Figure 5. Risk factors for methicillin-resistant *Staphylococcus aureus* carriage. From Sista et al. (45). Reprinted from *Anesthesiology Clinics of North America,* Vol 22, RR Sista, G Oda, and J Barr, Methicillin-resistant *Staphylococcus aureus* infections in ICU patients, Pages 405-435, Copyright (2004), with permission from Elsevier.

3.3.1.5 HA-MRSA contributions to increased morbidity and mortality

Obviously, any type of infection can cause an increase in morbidity and mortality. However, many studies have been conducted that compared the outcomes of patients infected with MRSA to patients infected with MSSA, each focusing on a specific infection type. In the case of SSIs, Engemann and colleagues found that patients with MRSA had a greater 90-day mortality rate and a greater length of hospitalization after the start of infection compared to patients with MSSA SSIs. In fact, the 90-day mortality adjusted odds ratio for MRSA versus MSSA patients with SSIs was 3.4 (95% CI, 1.5-7.2) and the median number of days hospital stay after infection was 15 days in MRSA patients versus 10 days in MSSA patients (56). In a

comparison of bacteremic patients, numerous increases in morbidity and mortality were found. MSSA bacteremic patients had longer ICU stays and ventilator dependency, a higher 30-day mortality rate (53% vs. 18%), and a higher in-hospital mortality rate (64% vs. 24%) than MSSA patients. With the data collected, the attributable mortality rates were calculated for MRSA bacteremia (23.4%) and MSSA bacteremia (1.3%); thus, MRSA bacteremia was found to have a significantly higher mortality rate (57). Similarly, a meta-analysis of ICU bacteremias found that patients with MRSA were two times as likely as patients with MSSA to die of bacteremia, with a risk ratio of 2.12 (58). The impact of MRSA in pneumonia patients has also been examined, but with conflicting results (45). Some studies have shown no increase in infection-related mortality, while others have shown a twenty-fold increase in risk (16, 59). It appears that the course of treatment may be key in reducing the risk in mortality for hospitalized MRSA pneumonia patients. In the study that found equal risks of mortality, a majority of patients were given vancomycin. However, in the study that found MRSA to be twenty times more deadly, β-lactam antibiotics were used to empirically treat patients until antibiotic sensitivity results came back. Vancomycin, while effective in treating both MSSA and MRSA, is known to have poor penetration of pulmonary tissues and slow bactericidal effects. On the contrary, β-lactam antibiotics are only effective for MSSA but have no problem penetrating pulmonary tissues and have average bactericidal effects (45). Thus, by administering vancomycin as a first-line agent for *S. aureus* pneumonia, physicians are helping MRSA patients gain effective treatment in a timely manner, but are not providing MSSA patients the most beneficial treatment.

3.3.2 Community-Associated MRSA epidemiology

3.3.2.1 Trends

3.3.2.1.1 Affected populations

In 1982, the first CA-MRSA outbreak was reported in the US (60). In a Detroit hospital from March to December of 1980, a group of physicians noticed a spike in MRSA infections that developed outside of the hospital. After some investigation of risks, they found that, of the 40 patients infected, 24 were intravenous (IV) drug users. However, it was not until the 1990s that CA-MRSA clusters were observed in other special population groups. It was during this period that outbreaks of infection became commonly observed among young children, Native American and Pacific Islander communities, prisoners, military personnel, men who have sex with men, and participants in professional and amateur sports (61).

3.3.2.1.2 Incidence estimates

Some relatively recent attempts to estimate the incidence of MRSA have been made, both in the US and abroad, but with the number of risk factors needed to exclude the HA-MRSA cases from the calculations, this can be a real challenge. In the United Kingdom (UK), however, where a socialized system of medical care allows investigators full access to 3.4 million patients' medical records that detail medical history and treatments received, it was estimated that in the adult population (aged 18 and over), the average incidence of CA-MRSA from 2000 to 2004 was 15.2 cases per 100,000 persons per year. Investigators noted an increase from 332 cases in 2000 to 484 cases in 2004 (62). Here in the US, a multi-location surveillance of invasive CA-MRSA was completed in 2005. In the US, it appears that invasive CA-MRSA varies hugely by geography; of the 9 locations reporting, the lowest incidence was found in Ramsey County, Minnesota, at 1.6 persons per 100,000 and the highest incidence was in Baltimore City,

Maryland, at 29.7 per 100,000. However, Baltimore was a great outlier compared to the other locations, which ranged from 1.6 to 6.8 per 100,000; thus the overall estimate for invasive CA-MRSA for these sites was 4.6 per 100,000 (interval estimate, 3.6-4.4) (13). Because the different criteria that were used to classify cases in the UK and US, with the UK having much better access to detailed medical history information used to ensure strict adherence to case definition, the two incidence rates cannot be compared.

3.3.2.1.3 Increases in jails and general population

There are many documented CA-MRSA outbreaks in the prison population. In a review of MRSA in prisoners, Aiello and colleagues found that San Francisco and Texas jails had reported similar large increases in methicillin-resistance over time (63). In San Francisco, the prevalence of MRSA among *S. aureus* isolates rose from 29% in 1997 to 74% in 2002. In Texas, the prevalence of MRSA among prisoners with *S. aureus* infections increased from 25% in 1998 to 66% in 2002. Interestingly, this increase in MRSA was also observed in a comprehensive study of the general population in the San Francisco area (52). In this study, investigators found that the number of unique MRSA isolates increased from 160 in 1996 to 563 in 2002. The number of HA-MRSA cases in hospitals and long term care facilities remained stable over this time; it was the CA-MRSA cases that had increased significantly, as shown below in Figure 6. In fact, it was calculated that 82% of the MRSA cases above the baseline could be attributed to CA-MRSA infection.

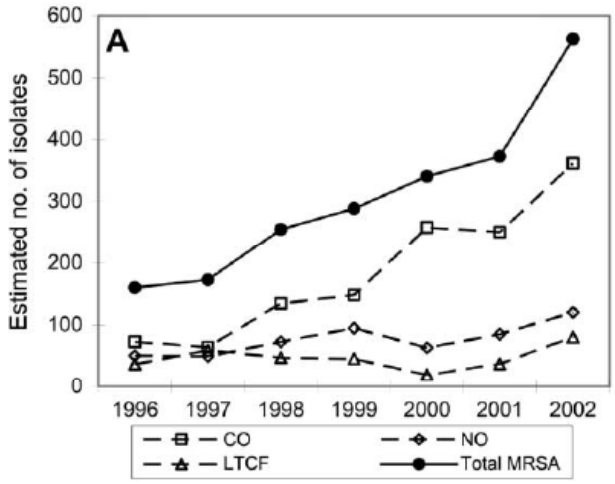


Figure 6. Estimated number of MRSA isolates from 1996 to 2002 in the San Francisco area, where CO is CA-MRSA, NO is HA-MRSA associated with hospitals, and LTCF is HA-MRSA associated with long term care facilities. From Carleton et al. (52).

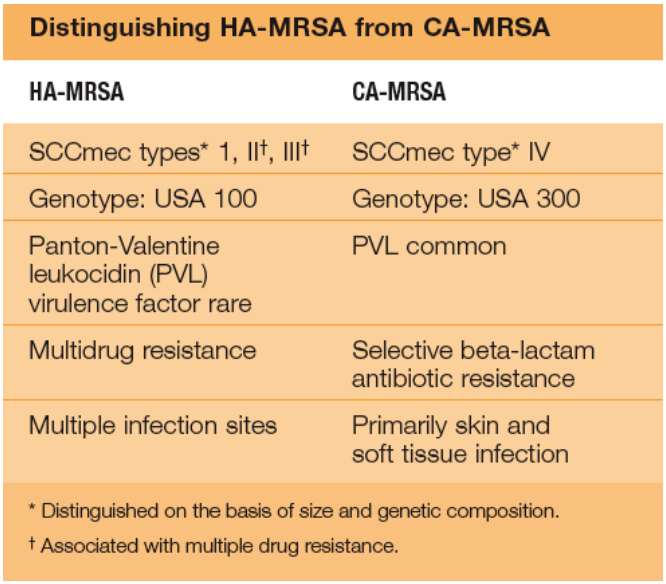
3.3.2.1.4 Increase in pediatric cases

Looking at CA-MRSA in children, an increasing trend is also shown. MRSA is a common infective agent seen in children seeking emergency care. At a Texas children's hospital emergency department from 2001 to 2004, the number of CA-MRSA infections increased by 2.2-fold; comparatively, CA-MSSA cases increased 1.7-fold. However, there were many more MRSA cases and than MSSA cases. Of the *S. aureus* isolates from community-associated infections during this three year surveillance period, 74% were MRSA (2659/3578). Researchers also observed a statistically significant increase in the proportion of MRSA isolates over those three years. In year one, 71.5% were MRSA, in year two, 73.5% were MRSA, and in year three, 76.4% were MRSA (p=.008) (64). From these observations in children and those in prisoners, the implications are that a reservoir of MRSA that is genetically distinct from common hospital strains exists in the community. In the late 1990s, there were two clusters of MRSA infection

among children lacking health care-associated risk factors—one in Chicago and one in Minnesota and North Dakota—that have given the community reservoir theory greater weight (35, 36).

3.3.2.2 Common strains of CA-MRSA detected

The PFGE strain most often associated with CA-MRSA cases is USA300, but USA400, 700, 1000, and 1100 have also been found to be causes of infections (13, 48). An overwhelming majority of CA-MRSA infections are caused by strains carrying SCC*mec* IV, one of the shorter SCC*mec* variations that is much less likely to carry multi-drug resistance (54). Many CA-MRSA strains also carry PVL genes. Both of these genetic elements have been shown to have a strong association with CA-MRSA infections and are not often present in HA-MRSA isolates. In a comparison of CA-MRSA to HA-MRSA isolates, odds ratios were calculated for the presence of SCC*mec* IV and PVL, yielding 5.87 (95%CI, 3.67-6.55) and 5.01 (95%CI, 3.49-5.25) respectively (50). One investigation showed that 95% of the CA-MRSA isolates in a particular health care system contained SCC*mec* type IV and 69% carried PVL genes (51). This genetic epidemiology explains why CA-MRSA infections have widely been characterized as causing skin infections and not having multiple drug resistance problems (19). Figure 7 shows a summary of characteristics used to distinguish CA-MRSA from HA-MRSA that was published to educate health care professionals.



Distinguishing HA-MRSA from CA-MRSA

HA-MRSA	CA-MRSA
SCCmec types* 1, II†, III†	SCCmec type* IV
Genotype: USA 100	Genotype: USA 300
Panton-Valentine leukocidin (PVL) virulence factor rare	PVL common
Multidrug resistance	Selective beta-lactam antibiotic resistance
Multiple infection sites	Primarily skin and soft tissue infection

* Distinguished on the basis of size and genetic composition.

† Associated with multiple drug resistance.

Figure 7. Summary of distinguishing characteristics for HA-MRSA and CA-MRSA. From Ragan (19). (Used with permission from JAAPA, Journal of the American Academy of Physician Assistants. Copyright is held by the American Academy of Physician Assistants and Haymarket Medical, Inc.)

Although CA-MRSA strains vary by geographic location, it appears that CA-MRSA strains have become less genetically diverse over time, with some strains dominating others because of environmental selective pressures (51). Kaplan and colleagues suggest that these selective pressures might lead to changes in a short period of time (64). In early 2000, they observed that roughly 50% of CA-MRSA isolates were USA300, but by 2003, more than 90% of CA-MRSA isolates were USA300. Others have also noted the emergence of a dominant MRSA clone in a community, so it may be a common phenomenon (65, 66).

3.3.2.3 Common clinical manifestations of CA-MRSA

The most common manifestation of CA-MRSA reported, by far, is skin and soft tissue infection (SSTI). Estimates of the percentage of CA-MRSA cases that are SSTI range from 59.3% (52) to 95.6% (64). However, most estimates fall somewhere between 75% and 80% (2,

15, 18, 50). Within the SSTI category, the most common type of infection observed is abscess. Of the CA-MRSA SSTIs seen at a Texas children's hospital, 59% were classified as abscesses (67); identically, in a three city study, a figure of 59% was also calculated from observations (15). However, cellulitis, folliculitis, and wound infections are also possible, with cellulitis being the second most common SSTI (15). CA-MRSA can also cause pneumonia, sometimes preceded by influenza-like illness (54). In one surveillance effort, it was estimated that pneumonia may comprise 2% of all CA-MRSA cases (15). In 2005, four cases of severe necrotizing CA-MRSA pneumonia were reported in Baltimore, Maryland (68). All four patients were previously healthy adults lacking typical risk factors for MRSA infection, and all were infected by the USA300 PFGE type with SCC*mec* IV and PVL genes. These were the first cases of this type reported in North America. Other types of infection possible but not as novel as necrotizing pneumonia include urinary and respiratory infections, which are estimated to represent about 9% and 12% of CA-MRSA cases, respectively (52). A small estimated percentage of CA-MRSA cases, 6%, are invasive, which includes bacteremia, septic arthritis, and osteomyelitis (15).

3.3.2.4 Risk factors for CA-MRSA

Ironically, the people found to be most at risk of developing a CA-MRSA infection are young and healthy people who lack health care risk factors. Studies comparing people infected with CA-MRSA versus people with HA-MRSA have consistently found that CA-MRSA patients are significantly younger. In particular, a study by Crum and colleagues found that CA-MRSA patients had a median age of 22 years, compared to the median age of 64 years observed in HA-MRSA patients (51). But, considering this data was collected from a military hospital, serving a large population of younger people and their families, these figures may not be generalizable to

other populations. In another study with a broader population, investigators found the median age to be 23 for CA-MRSA patients compared to a median age of 68 years for HA-MRSA patients (50). Even when cases from the two participating pediatric hospitals were excluded from the analysis, the median age of CA-MRSA patients was still significantly lower than HA-MRSA patients (30 versus 70 years, $p<0.001$).

In addition to age, race has also been compared between people with CA-MRSA and CA-MSSA. In a study by a group in Texas, it was found that African American children represented a disproportionately high number of CA-MRSA cases (67). When the group looked more closely at demographic characteristics for the racial groups, they saw no significant differences in type of health insurance, proportion attending day care, chronic illness, use of antibiotics within the previous six months, previous hospitalization, or exposure to health care workers or nursing home residents. Thus, little explanation has been given on why this difference exists. Later studies would replicate these results. In another Texas study at the same children's hospital, investigators found once again that African American children were more likely than children of other racial groups to develop CA-MRSA, as shown in Table 2 below (64). In an Atlanta study, incidence rates were also found to be significantly higher in African Americans than in whites (RR=2.74, 95%CI 2.44-3.07) (15).

Table 2. Racial and ethnic distribution of cases of CA-MRSA and CA-MSSA. Adapted from Kaplan et al. (64).

Patient Race/Ethnicity	MRSA Total Number, (%)	MSSA Total Number, (%)
Asian	34 (1.3%)	33 (3.6%)
African American	1045 (39.3%)	249 (27.1%)
White	681 (25.6%)	259 (28.2%)
Hispanic	788 (29.6%)	302 (32.9%)
Other	86 (3.2%)	60 (6.5%)
Unknown	25 (0.9%)	16 (1.7%)

Underlying health conditions among CA-MRSA patients have been examined for commonalities. In children, the most common underlying condition is a dermatological condition. Of CA-MRSA cases in two studies, researchers found that 9% of children had eczema or some other dermatological condition (50, 67). Another underlying condition that is commonly reported, about as often as dermatological conditions, is asthma (15, 67). However, Sattler and colleagues found that asthma was reported as frequently in the MSSA patients, suggesting that it does not play a significant role in increasing risk of MRSA. In adults with CA-MRSA infections, the underlying conditions reported most often are tobacco use (19-35%) and diabetes (17-19%) (15, 50). However, while tobacco use is reported, there have been no suggestions that it increases the general risk of CA-MRSA infection. Close behind tobacco use and diabetes comes the risk increase due to previous skin infection or dermatological conditions. Naimi and colleagues found that 13% of cases had dermatological conditions (50), and Fridkin and colleagues found that 21% of cases had previous skin infection (15).

It has also been suggested that previous antibiotic use may lead to increased risk of CA-MRSA infection. One study from the UK found an apparent dose-dependent relationship between antibiotic use and infection that varied by antibiotic class (62). The strongest increase in risk was found with quinolones (adjusted OR=3.37, 95%CI 2.80-4.09) and macrolides (adjusted OR=2.50, 95%CI 2.14-2.91). These findings are somewhat supported by a recent meta-analysis that examined previous antibiotic use as a risk factor for MRSA infection (69). In the meta-analysis, it was calculated that quinolones provided the highest increase to risk of infection (RR=3, 95%CI 2.5-3.5); macrolides were only found to increase risk in one study evaluated by the authors, so they were not reported as a risk factor. Also in the meta-analysis, a risk ratio was calculated for general antibiotic use in raising the risk of CA-MRSA and was

found to be 1.6 (95%CI 1.5-1.7). Despite this evidence of antibiotic use as a risk factor, though, investigators in the UK study noted that a great percentage (38.9%) of patients included in this study who developed CA-MRSA infection had not taken antibiotics in the year before their infections.

General exposure to health care has also been identified as a potential risk factor for developing CA-MRSA. By the CDC-recommended definition, for a case to be considered community associated, the patient cannot have been hospitalized in the past year (42). However, some surveillance efforts classify by the time of sample collection only, defining CA-MRSA as an infection developing in an outpatient setting or within 72 hours of admission to the hospital. In one study using this loose definition, Carleton and colleagues found that 65.2% of CA-MRSA patients had been hospitalized in the past 2 years and 25.4% had been treated in an outpatient setting (52). Only 9.4% patients who fit their definition of CA-MRSA lacked a history of health care exposure in the two years prior to infection. However, because risk factors were not taken into account when classifying the infections as CA-MRSA, this seems likely to be an exaggeration of the effect that contact with health care has on risk of CA-MRSA infection, as an unknown number of the "CA-MRSA cases" may have had medical histories that should have excluded them from the category.

Similar to hospital settings, where MRSA is known to spread from person to person, CA-MRSA has been observed to spread within families and between other groups of people in close contact, such as children in day care, prisoners, and athletes in contact sports. One study found that having a family member with MRSA increases the risk of developing MRSA (51). In 2004, of the 632 MRSA isolates analyzed at one hospital (including both HA- and CA-MRSA), 63 (10%) were among family members and all of these 63 were classified as CA-MRSA. In a day

care setting, after one child developed a serious MRSA middle ear infection, his classmates and the day care staff were tested for MRSA carriage (12). Of the 164 classmates and 9 staff members, only 1 classmate was colonized with MRSA. After further investigation, the classmate's sister was also found to be colonized, and PFGE analysis found that strains for all three children were identical to each other and very different from the hospital strains common to that geographic area. While it could not be determined from this case study which child first had MRSA colonization, it strongly suggests person to person spread is common in families and at day care. Similarly, PFGE pattern analysis during prison MRSA outbreaks have found that all isolates were indistinguishable, suggesting person to person spread (63), as well as among athletic teams, both professional and amateur (70). In sports, people who play positions requiring frequent, repetitive contact have the most increased risk of infection due to skin injury.

3.3.2.5 CA-MRSA contributions to increased morbidity and mortality

Some severe outbreaks of CA-MRSA have been reported, gaining much attention from the media. One particular outbreak reported in 2000 among members of a Pennsylvania college football team resulted in 7 of 10 infected players being hospitalized and treated with intravenous antibiotics (40). Not all infections have these serious outcomes. However, when comparing the effects of CA-MRSA to CA-MSSA, it does appear that methicillin-resistant strains cause greater morbidity and mortality. One study found a statistically significant difference between the hospitalization of children with CA-MRSA (62%) than children with CA-MSSA (53%) (64). Another surveillance effort of the general population found that 24% of all patients with CA-MRSA were hospitalized due to infection, and 5% of all CA-MRSA patients required intensive care (50). Similarly, a study by Fridkin and colleagues found that 24% of CA-MRSA patients interviewed (136/575) had been hospitalized as a result of their infections (15).

4.0 ORIGINAL RESEARCH

In September of 2007, while exploring the possibilities for designing a practicum that would allow me to investigate an infectious disease-related topic, I contacted the Allegheny County Health Department (ACHD). Dr. LuAnn Brink, the epidemiology manager, brought forth an idea involving a project using a database of people who had positive methicillin-sensitive *S. aureus* and MRSA cultures that had recently been reported to ACHD. At that time, reporting of MRSA was only mandatory in pediatric cases, but ACHD was about to institute across the board mandatory reporting for all positive cultures to gain a clearer picture the incidence of infection and the populations most at risk in the county. Thus, the data that I would explore would offer another snapshot of the disease before mandatory reporting. With the approval of ACHD Director, Dr. Bruce Dixon, and the Department of Infectious Diseases and Microbiology at the University of Pittsburgh's Graduate School of Public Health, I undertook this project.

5.0 METHODS

Quest Diagnostics provided a database consisting of 1005 people with MRSA (cases) and 1219 people with methicillin-sensitive *S. aureus* (MSSA) (controls). This cohort of 2224 was used to conduct a case-control study to determine differences in epidemiology of the infections between the two groups. From this initial group, 19 cases and 7 controls from the Allegheny County Correctional Facility were excluded, leaving 986 cases and 1212 controls. The database consists of patients who sought medical care in Allegheny County, Pennsylvania from January 1, 2007 to August 31, 2007 and had samples that cultured positive for MRSA or MSSA, as confirmed by the laboratory results from Quest. Many of these individuals may have acquired the infections outside of healthcare settings. However, some of the health care providers who collected patient samples and sent them to Quest for analysis are long-term care facilities.

From this database, two random 10% samples of cases and controls were taken using Statistical Package for the Social Sciences (SPSS) software. SPSS selects random samples based on a pseudo-random-number generator that depends on a seed value established by the program (71). Patients' phone numbers were located by address using the 2008 COLE Directory. If the address was not located in the Directory, the address' validity was assessed using the Allegheny County Property Tax Assessment website. If the address did not exist, nothing more was done; if the address did exist, yellowpages.com was used in a last attempt to locate a phone number by address and name. Before contacting each patient, the physician who requested the laboratory

test was first contacted as a courtesy. Next, each patient was contacted by phone between the hours of 10 A.M. and 4 P.M., Monday through Friday during November 2007 to January 2008. If a patient was not home, a message requesting that they call the health department was left on the machine or with a family member, if possible. Patients not reached after three call attempts were considered non-responsive. When a patient was reached, they were interviewed using a standardized questionnaire that collected basic demographic information, clinical information about the infection and treatment received, and risk factors (see Appendix A). If the patient was at a long-term care facility at the time when the sample was taken, a member of the medical staff with access to patient charts was interviewed for interview completion.

After the first 10% sample (cases, n=97; controls, n=107) from each group was exhausted, a second random 10% sample (cases, n=82; controls, n=89) was taken using SPSS. First, any duplicates from the first sample were eliminated. Then, the same procedure used with the first sample group was followed in contacting this second sample of patients. Once fifty questionnaires had been completed for cases and for controls, calling ceased. Any patients who returned calls within a day after the quota was met were interviewed and their answers were included in the analysis of results.

Information collected during interviews was recorded in a deidentified format. Data was entered and counts were calculated using SPSS (Mac Version 16.0). Chi-square and Fisher exact tests were used for comparisons of categorical variables and the Student t-test was used for age comparisons. All responses of “unknown” and “not applicable” were excluded from the categorical analyses. All confidence intervals were calculated at 95%.

6.0 RESULTS

6.1 ANALYSIS OF STUDY POPULATION

The reporting laboratory provided ages and genders for all individuals in the database. This allowed a comparison of all reported cases and controls. When compared to the controls, the MRSA cases were older. The mean age for MRSA cases was 47.7 (CI 45.9-49.5) years, while MSSA controls had an average age of 39.8 (CI 38.3-41.4). An independent t-test showed a statistically significant ($p<0.001$) mean difference of 7.9 years (CI 5.5-10.2). This difference in means is also reflected in distribution of cases by age. The MRSA group had a greater proportion of older people than the control group. In fact, 34.4% of MRSA cases were aged 65 years or older; only 22.1% of MSSA controls were in that same age range. The age distribution of the population affected by MSSA seems be more representative of the local population than the age distribution of the population affected by MRSA. The median age of MSSA controls was 39 years, much closer to the estimated median age of 41.7 years for the population of Allegheny County than the 50 year median age of MRSA cases (72). Gender distribution was similar between groups. The MRSA cases consisted of 55.1% females and 44.5% males, while MSSA controls consisted of 53.4% females and 46.1% males.

6.2 COMPARISON OF STUDY POPULATION TO RESPONDENTS

Similar to the database population, among the people who completed the questionnaires, MRSA respondents (n=54) were older than MSSA respondents (n=50). However, both groups of respondents were older than the database population as a whole (Figures 8 and 9). The mean age differences in the MRSA and MSSA groups were 6.6 and 8.7 years respectively. The 8.7 year difference between the MSSA respondents and the database population indicates a statistically significant difference in age (p=0.0283); the age difference between MRSA respondents and the MRSA database population, however, was not significant (p=0.0986). Comparing respondent groups, the average age of MRSA respondents was 54.4 years and MSSA respondents was 48.5 years; unlike the database populations, this is not a statistically significant difference (p=0.292). The median ages for cases and controls were 57 and 54 years, respectively. MRSA respondents consisted of 51.2% males and 48.2% females. MSSA respondents were 34% male and 66% female, a statistically significant imbalance from the expected 1:1 ratio (2-sided binomial, p=0.033).

As shown in Table 3, a large majority of respondents self-classified their race as white or Caucasian; other groups represented are black or African American, and Asian. Nine respondents did not indicate a racial group. A majority of questionnaires were completed by patients, but some were answered by patients' parents or other knowledgeable caretakers, patient's spouses, or medical staff. In some instances, medical staff answered questionnaires on behalf of patients who were deceased or had left the facility. At the time that the sample was taken and sent to Quest, 27.8% of cases and 10% of controls were in non-hospital, non-prison community living settings (CLSs). CLSs include any group or communal living situations that are not a hospital or prison, including skilled nursing facilities, assisted living facilities and group

homes. At the time of interview completion, 83.3% of cases and 96% of controls were alive; 11.1% of cases and 2% of controls were deceased. Additionally, 5.6% and 2% of cases and controls, respectively, had left the CLSs and their vital status at the time of interview could not be determined.

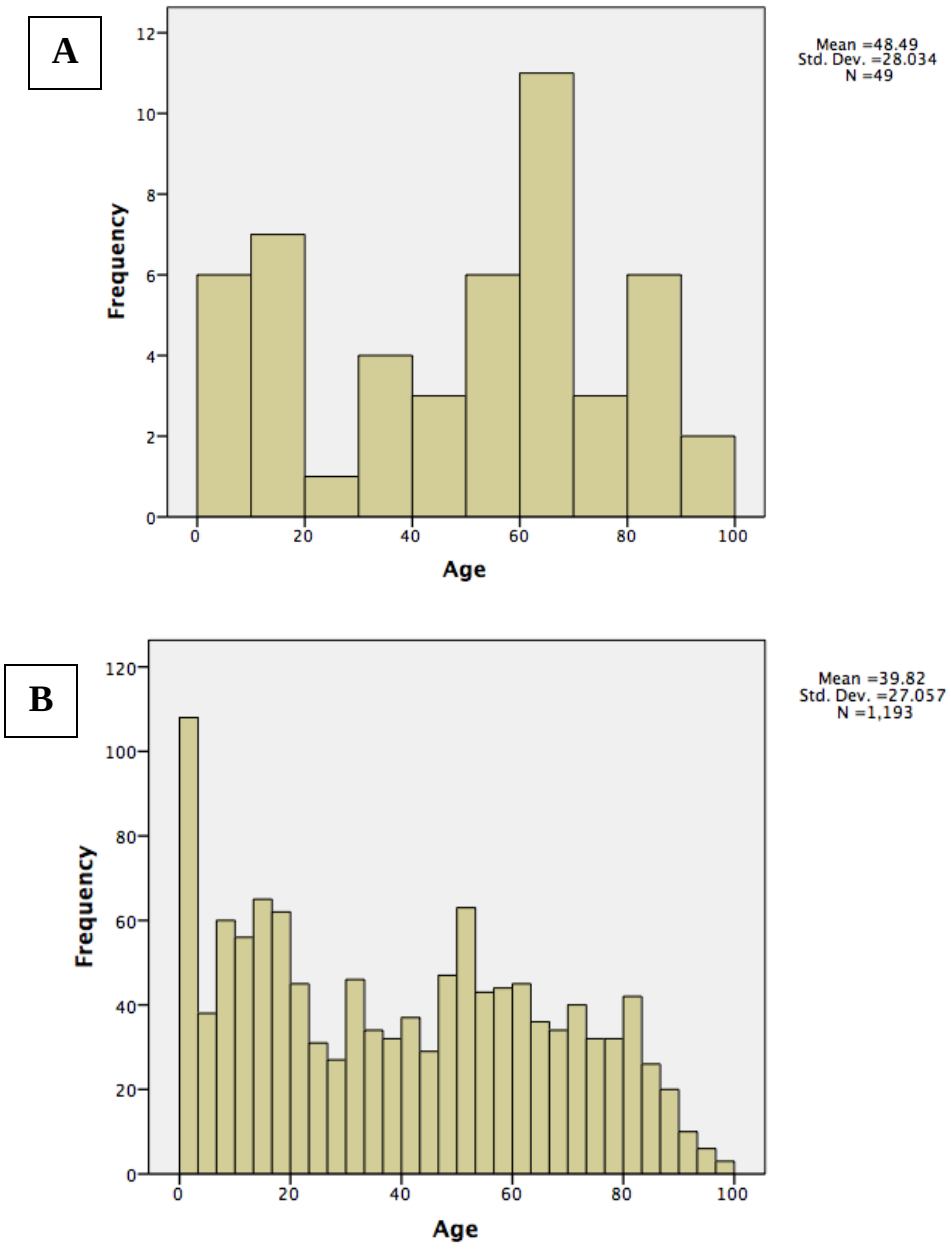


Figure 8. Histograms of ages of MSSA respondents (A) and MSSA database (B).

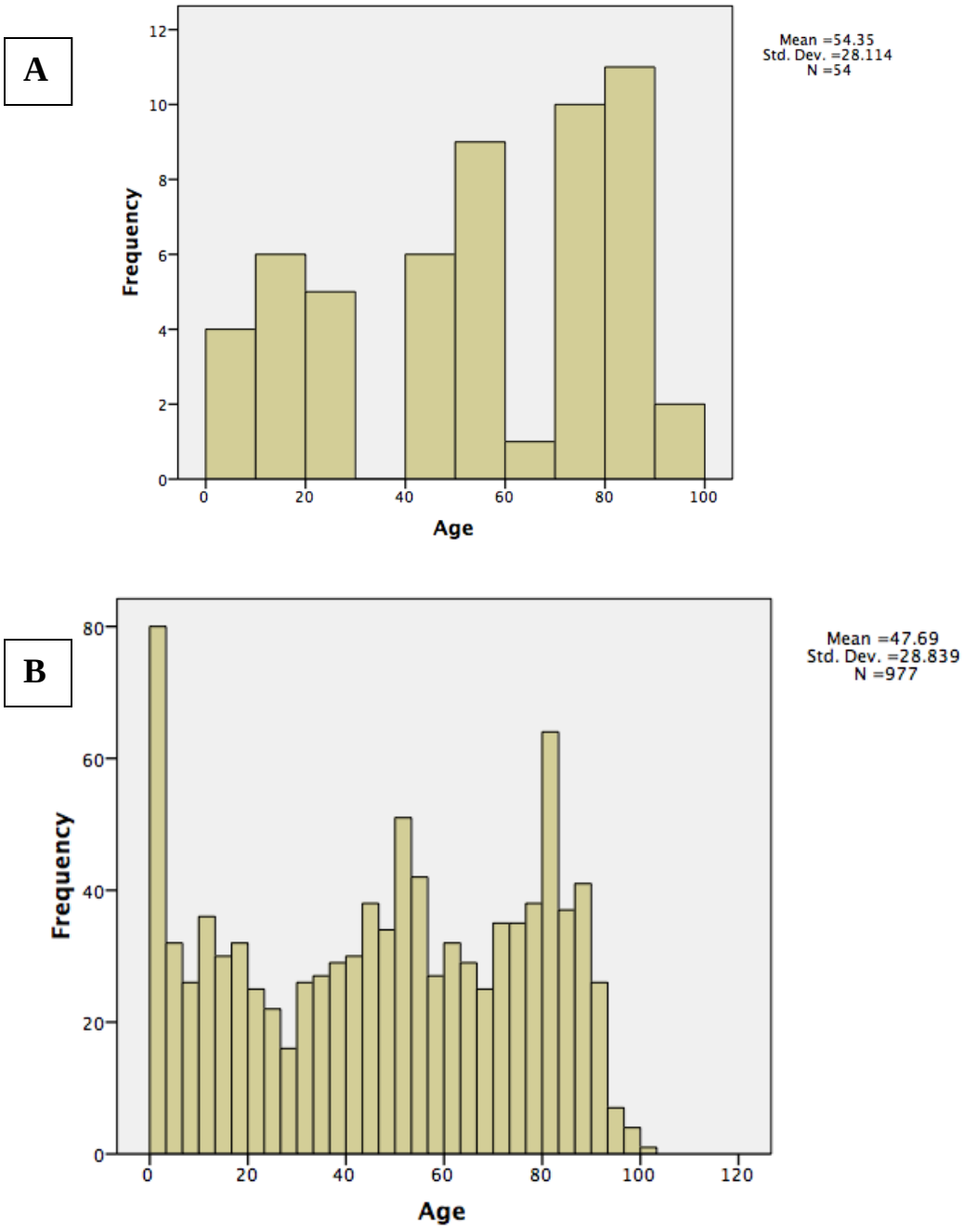


Figure 9. Histograms of ages of MRSA respondents (A) and MRSA database (B).

Table 3. Respondent characteristics.

	MRSA (n=54)	MSSA (n=50)	p-value
Age			
Mean (SD)	54.4 (28.0)	48.5 (28.0)	0.292
Median	57	54	
Sex			
Male	28 (51.2%)	17 (34.0%)	0.066
Female	26 (48.2%)	33 (66.0%)	
Race			
White/Caucasian	42 (77.8%)	44 (88%)	
Black/African American	4 (7.4%)	4 (8%)	
Asian	1 (1.8%)	0 (0%)	
Pacific Islander	0 (0%)	0 (0%)	
Native American	0 (0%)	0 (0%)	
Other	0 (0%)	0 (0%)	
No Response	7 (13.0%)	2 (4%)	
Vital Status			
Living	45 (83.3%)	48 (96%)	0.112
Deceased	6 (11.1%)	1 (2%)	
Unknown	3 (5.6%)	1 (2%)	
Completed by			
Patient	27 (50%)	31 (62%)	
(95% CI)	(36.8-63.1%)	(48.0-74.6%)	
Parent/Caretaker	9 (16.7%)	14 (28%)	
(95% CI)	(8.4-28.4%)	(16.9-41.6%)	
Spouse	2 (3.7%)	0 (0%)	
(95% CI)	(0.6-11.7%)	(0.0-5.8%)	
Medical Staff	16 (29.6%)	5 (10%)	
(95% CI)	(18.6-42.7%)	(3.8-20.8%)	
In CLS When Sample Was Taken			
Yes	15 (27.8%)	5 (10%)	0.481
No	39 (72.2%)	45 (90%)	

Evaluating disease characteristics and treatment required for cases and controls (Table 4), MRSA samples were more likely to have been taken from the skin than MSSA (70.4% versus 58.0%). Most other categories of sample sites seemed similar between the cases and controls, except the eye, which was more common in the MSSA group (8.0%) than in the MRSA group (1.8%). As for the infection type, MRSA respondents were more likely to classify their infection as an abscess (44.4%) than the MSSA respondents (32.0%). MRSA respondents were only slightly more likely than MSSA respondents to have been prescribed antibiotics as treatment (81.5% versus 78.0%). Five MRSA respondents (9.2%) and three MSSA respondents (6.0%) reported being hospitalized as a result of their *S. aureus* infection.

Table 4. Disease characteristics and treatment.

	MRSA	MSSA	p-value
Sample Source Location			
Skin, General	38 (70.4%)	29 (58.0%)	-
Genital	1 (1.8%)	2 (4.0%)	-
Nares	3 (5.6%)	1 (2.0%)	-
Urine	7 (13.0%)	8 (16.0%)	-
Eye	1 (1.8%)	4 (8.0%)	-
Upper Respiratory	2 (3.7%)	2 (4.0%)	-
Lower Respiratory	0 (0.0%)	1 (2.0%)	-
Blood	1 (1.8%)	0 (0.0%)	-
Other	1 (1.8%)	2 (4.0%)	-
Unknown	0 (0.0%)	1 (2.0%)	-
Type of Infection			
Abscess	24 (44.4%)	16 (32.0%)	-
Folliculitis	2 (3.7%)	0 (0.0%)	-
Cellulitis	0 (0.0%)	0 (0.0%)	-
Other	23 (42.6%)	29 (58.0%)	-
No Infection	4 (7.4%)	3 (6.0%)	-
Unknown	1 (1.8%)	2 (4.0%)	-
Treated with Antibiotics			
Yes	44 (81.5%)	39 (78.0%)	0.198
No	1 (1.9%)	4 (8.0%)	
Unknown	5 (9.2%)	5 (10.0%)	
N/A	4 (7.4%)	2 (4.0%)	
Hospitalized			
Yes	5 (9.2%)	3 (6.0%)	0.714
No	43 (79.6%)	45 (90.0%)	
Unknown	2 (3.7%)	0 (0.0%)	
N/A	4 (7.4%)	2 (4.0%)	

Table 5. Evaluation of risk factors in respondents, where * indicates a p-value<0.05.

	MRSA	MSSA	p-value
Reported Self History of MRSA			
Yes	15 (27.8%)	1 (2.0%)	<0.001*
No	33 (61.1%)	48 (96.0%)	
Unknown	6 (11.1%)	1 (2.0%)	
Household Member or Self with MRSA			
Yes	10 (18.5%)	2 (4.0%)	0.006*
No	33 (61.1%)	47 (94.0%)	
Unknown	11 (20.4%)	1 (2.0%)	
Household Member or Self in Hospital			
Yes	24 (44.4%)	13 (26.0%)	0.041*
No	28 (51.8%)	36 (72.0%)	
Unknown	2 (3.7%)	1 (2.0%)	
Household Member or Self in CLS			
Yes	16 (29.6%)	6 (12.0%)	0.032*
No	38 (70.4%)	43 (86.0%)	
Unknown	0 (0.0%)	1 (2.0%)	
Previous Antibiotic Use			
Yes	31 (57.4%)	25 (50.0%)	0.154
No	14 (25.9%)	21 (42.0%)	
Unknown	9 (16.7%)	4 (8.0%)	
Outpatient Surgery			
Yes	0 (0.0%)	2 (4.0%)	0.227
No	51 (94.4%)	45 (90.0%)	
Unknown	3 (5.6%)	3 (6.0%)	
Play Sports			
Yes	9 (16.7%)	7 (14.0%)	0.706
No	45 (83.3%)	43 (86.0%)	
Piercing			
Yes	0 (0.0%)	1 (2.0%)	0.485
No	53 (98.1%)	49 (98.0%)	
Unknown	1 (1.9%)	0 (0.0%)	
Tattoo			
Yes	0 (0.0%)	0 (0.0%)	-
No	53 (98.1%)	50 (100.0%)	
Unknown	1 (1.9%)	0 (0.0%)	
Chronic Disease			
Yes	31 (57.4%)	26 (52.0%)	0.580
Diabetes	10 (18.5%)	7 (14.0%)	0.534
Skin Condition	5 (9.2%)	3 (6.0%)	0.717
No	23 (42.5%)	24 (48.0%)	
HCW in Household			
No HCW	34 (63.0%)	40 (80.0%)	0.563
HCW with Patient Contact	4 (7.4%)	4 (8.0%)	(pooled)
Non-HCW with Patient Contact	0 (0.0%)	1 (2.0%)	
HCW with no Patient Contact	1 (1.8%)	0 (0.0%)	
N/A	15 (27.8%)	5 (10.0%)	

Examining risk factors for developing MRSA rather than MSSA, there were four that had statistical significance. The first two were having a reported self history of MRSA ($p<.001$) and having a household member or self with MRSA in the year prior to positive culture results ($p=.006$). The third and fourth risk factors of statistical significance were having a household member or self being hospitalized in the year prior to positive culture results ($p=.041$) and having a household member or self in a CLS in the year prior to positive culture ($p=.032$). All other risk factors evaluated did not show statistical significance (Table 5).

7.0 DISCUSSION

In this retrospective study, there were several potential risk factors identified when MRSA-positive patients were compared to MSSA-positive patients. These factors included having a reported self history of MRSA ($p<.001$), having a member of the household or self with a MRSA infection in the year prior to infection ($p=.006$), having a member of the household or self hospitalized in the year prior to infection ($p=.041$) and having a member of the household or self in a CLS in the year prior to infection ($p=.032$). None of these identified risk factors were novel as they have been previously identified as such in other studies. Nonetheless, this research serves as a confirmation of existing literature.

We intended to capture a clearer picture of MRSA in the communities of Allegheny County, Pennsylvania, outside of hospitals, prisons, and CLSs. However, it is clear that people in CLSs with MRSA have been included, with 15 of 54 (27.8%) MRSA-positive respondents and 5 of 50 (10.0%) MSSA-positive respondents having been in CLSs at the time of the samples being taken. Knowing that a greater number of the MRSA respondents were in CLSs such as nursing homes than MSSA respondents, it follows that the MRSA respondents were older than MSSA respondents by an average of 5.9 years. This is similar to the results found by Kuehnert and colleagues that age was a risk factor for having MRSA colonization of the nose (22). This considerable number of people who were in CLSs may have also influenced the significance of risk factors. Examining the responses of those who said that they or a household member had

been hospitalized in the year prior to infection versus those who said that they or a household member had been in a CLS in the year prior to infection, 18 of 37 people (48.6%) with hospitalization had also been in CLSs. Of the 20 people in CLSs, 18 of them (90%) had also been hospitalized, indicating a great deal of relatedness between the two risk factors. In fact, if people in CLSs at the time of the sample being taken are excluded from the analysis (Table 6), hospitalization in the prior year is no longer a significant risk factor for being MRSA-positive (p=.410).

Table 6. Hospitalization as risk factor with CLS patients excluded.

		MRSA	MSSA
Hospitalization	Yes	11	9
	No	28	35

Another set of risk factors that are closely related in this study are having a reported self history of MRSA and having a household member or self with MRSA infection in the past year. This is similar to the findings of the previously mentioned study, where Crum and colleagues found that 13% of all patients included in their study had multiple positive MRSA cultures and 69% of these cultures represented recurrent infections (51). In our study, of 104 respondents, 12 said that they or a household member had a MRSA infection in the year prior to their sample being taken. Of those 12, 10 people identified themselves as having the MRSA infection; only 2 people did not have the infection themselves. Of the 16 people who identified themselves as having a history of MRSA, 10 said that they had an infection in the last year, 5 had no infection in themselves or a household member in the past year, and 1 could not remember. Thus, the

most likely risk factor seems to be that once a person is infected with MRSA for the first time, they are more likely to develop another infection in the following year. However, from the data collected, it cannot be determined if the repeated infections that people developed were recurrent or at a new site; this could be explored in future work. The challenge of preventing repeated infection has been explored previously. Researcher J.M. Boyce shared that even after the infection clears, colonization at alternate sites of the body may remain, especially in the nose where antimicrobial activity may be minimal in the nasal secretions, increasing the risk of repeat infections (73).

A previous investigation linked MRSA infections to recently receiving a tattoo (39); however, in our study, none of the respondents had recently received a tattoo. Other studies, including a meta-analysis (69) linked previous exposure to antibiotics to an increased risk of MRSA; the meta-analysis found that people exposed to antibiotic therapy had an almost 2-fold chance of acquiring MRSA than non-exposed people. However, from the data collected for Allegheny County, antibiotic use was fairly common in both groups, with no statistically significant difference between MRSA and MSSA respondents ($p=.154$). Additionally, most people interviewed could not recall what types of antibiotics they had taken previously, so no subgroup analysis could be performed to analyze which specific antibiotic classes were more closely linked with MRSA. Previous studies had found that quinolones and glycopeptides caused the greatest increases in risk of MRSA (69).

Another risk factor that has been identified in previous research is having chronic conditions, especially dermatological conditions (50). In the Allegheny County data, 31 of 54 (57.4%) MRSA respondents and 26 of 50 (52.0%) of MSSA respondents reported having chronically managed conditions, a non-significant difference ($p=.580$). Looking specifically at

skin conditions, 5 of 54 (9.2%) MRSA respondents and 3 of 50 (6.0%) MSSA respondents reported having skin conditions, which was not a statistical difference (p=.717). Diabetes is another commonly reported chronic condition that has been associated with MRSA (45), but it failed to be significant in this study (p=.534).

One of the biggest limitations of this study is recall bias. One problem very common in the interviews was that people were unsure of many details. Some people were contacted more than a year after the date when the sample was taken. Thus, some information that could have been examined, for example, treatment given for the infection and the length of treatment, was not available because many people declined to respond on account of uncertainly. For people with extensive medical histories and many trips to the doctor and hospital, it was hard to recall the specifics of their infection and assess the risk factors before the infection, such as hospitalization in the year prior. Some people with repeated infections had difficulty remembering the details of that particular incident. Also, some people were not aware of the results of the culture, making it harder to recall what happened. Because the database included all positive culture results—with no differentiation between light growth/colonization and heavy growth/infection—some people contacted did not have an infection. There were even some nasal cultures that were taken as surveillance measures in long term care facilities that were included in the database.

A second limitation of this study is the method by which patients were contacted for interview. First, all call attempts were made on weekdays between the hours of 10 A.M. and 4 P.M. Messages were left, when possible, and some people called back to complete the interview, but the completion of interviews only during these hours made it more difficult to reach middle aged working people. On the other hand, older, retired people were easier to reach. Second,

only people with published phone numbers were contacted, meaning that anyone who requested to be excluded from the directory or pays to have an unpublished phone number could not be reached. If an incorrect address was given, the person also could not be reached. Third, younger people and people who are less established were less likely to be reached. Because of the wide availability and affordability of cellular phones, many younger people may choose not to have a phone line at their home. Even if they choose to have a line, if they live in an apartment or had just moved to a new address, it is likely they are not included in the directory. The sum of all these factors is that, despite the steps taken to ensure random samples of the database populations, the people completing the interviews for this study did not have the same age distribution of the people in the databases. In particular, the youngest age groups were underrepresented in both the MRSA and the MSSA respondent groups. As illustrated in Figures 8b and 9b, children aged three years and younger were the highest frequency age group for people in the MRSA and MSSA databases. However, of the respondents, represented in Figures 8a and 9a, older people were represented with the highest frequencies. Thus, the people examined in this study were older and may vary in other unknown ways from the database population, giving biased results. One final limitation of this study is that a small number of surveys were completed, which resulted in a diminished ability to detect statistical differences.

In future studies, it would be helpful to exclude any persons who had samples taken while they were in CLSs and samples that indicated only colonization rather than infection. This would allow a better characterization of MRSA in the community and a clearer assessment of risks. Some areas that could be explored include comparing the severity of outcomes between the MRSA and MSSA groups. In this study, patients were asked which antibiotics they received as treatment and the length of treatment; however, it would be a stronger measure of severity if

patients were also asked specifically if they had intravenous (IV) antibiotics, how long their hospital stays were, and if intensive care treatment was required. In this study, some respondents did indicate that they received IV antibiotics, but most of those people had many chronic conditions and were already living at skilled nursing facilities, so it does not seem appropriate to use IV antibiotics as a measure of infection severity. Another topic that could be pursued in the future is tracking and comparing treatments in the MRSA and MSSA groups. Recall was a definite problem in this study because of the lag between samples being taken and follow-up calls being made, so future investigations would need to be much more timely to minimize the problem. Many MRSA respondents recalled being switched one or more times to different antibiotics, so it would also be interesting to examine which antibiotics area physicians are commonly prescribing and how quick they are to follow up with patients after receiving the lab results, ensuring that proper treatment is being giving as soon as possible to prevent infection progression.

8.0 PUBLIC HEALTH SIGNIFICANCE

There are several key implications for the effects of MRSA, both in the community and hospitals. As stated earlier, the best estimate of MRSA nasal colonization prevalence in the US population, measured in 2001-2002, stands at 0.8% (22). However, because colonization can occur at other sites (23-25), this is likely to be an underestimation of total population prevalence at that time. And, if the trends of the past continue to hold true, it can be assumed that the incidence of MRSA infections has continued upward since 2001. This continual increase in MRSA infections, especially outside of hospitals, suggests that the reservoir of MRSA in the community is growing with the passage of time. This idea of a reservoir of MRSA strains not associated with hospitals has already been explored by Carleton and her colleagues in the San Francisco population (52). They found that four clonal types were responsible for community-associated infections in patients who had previous contact with the health care system, either through hospitalization or outpatient services. If these clonal types were hospital-endemic strains, it would be expected that they cause a great number of infections that onset in hospitals; however, this was not the case. Thus, Carleton and colleagues have suggested that while the risk of MRSA infection is greater in people with health care contact, these people are not acquiring the MRSA bacteria during health care visits.

With the establishment of a CA-MRSA reservoir in the community, it is a real threat that these strains could end up establishing themselves in hospitals also. One previously mentioned

study found that MRSA stains carrying SCC*mec* IV were most likely to be causes of infection the community (>95% of MRSA isolates), but were being increasingly found as a cause of infection in the hospitals (52% of MRSA isolates) (52). This suggested that the community strains were becoming established in the hospitals and causing infection.

In addition to this reservoir of CA-MRSA strains, there are still the already existing reservoir of HA-MRSA strains found in long-term care facilities and hospitals. A considerable percentage of the US population is hospitalized each year, creating the possibility that HA-MRSA strains are brought into the community, resulting in infections. With the number of older Americans continuing to increase, the number of people in and out of hospitals and long term care facilities will undoubtedly increase also, creating greater rates of infection in the population. Since older people also have more chronic diseases and weakened immune systems, they may be more likely to serve as carriers of the bacteria for longer periods of time than healthy people. This increased length of carriage will create more opportunities for person to person spread, which could lead to increased rates of infection.

All of these increases result in corresponding increases in morbidity and mortality resulting from MRSA infection. As discussed earlier, MRSA often infects the skin and soft tissue. Recent studies have shown that MRSA is the most identifiable cause of acute skin and soft tissue infections seen in urban emergency departments(10), indicating the seriousness of these infections and the immediate treatment they require. All MRSA infections, especially if not treated appropriately, may become invasive, resulting in long hospital stays, with intensive care if necessary.

APPENDIX

ALLEGHENY COUNTY HEALTH DEPARTMENT MRSA CLINICAL DATA QUESTIONNAIRE

Questionnaire answered by: Patient ___ Parent of Patient ____ Medical Staff ____ Spouse___

Patient Information

Sex: Male ___ Female ___ DOB ___/___/_____ (mm/dd/yyyy)

Race: White ___ Black ___ Hawaiian Native/Pacific Islander ___ Asian ___
American Indian/Alaskan Native ___ Other ___ Refused___

Ethnicity: Hispanic ___ Non-Hispanic___ Not Answered___

Vital Status: Living ___ Deceased ____ Unknown____

Medical Information

When did you notice your infection? ___/___/_____ (mm/dd/yyyy)
Have you had a MRSA infection in the past? Yes ___ No___
What type of infection did you have? Abscess ___ Cellulitis ___ Folliculitis ___
Other _____
Where was the infection located (arm, leg, etc)? _____
Were you hospitalized for your infection? Yes ___ No____
Was your wound drained? Yes ___ No____
Were you treated with antibiotics? Yes ___ No____
If yes, which antibiotic? _____ Dose _____ (mg) # Days _____
If treatment is completed, are the signs and symptoms gone? Yes ___ No ___
If no, please explain _____
If no, do you plan on seeing your health care provider? Yes ___ No ___
Do you play any team sports or participate in an organized fitness activity? (List)
_____
If yes, did you continue to play with the infection? Yes ___ No___
Are these sports part of a school program? Yes ___ No___
If no, location of activity _____
In the year prior to your infection:
Did anyone in your household have a MRSA infection? Yes ____ No ____

If yes, who? _____

Were you, or was anyone in your household incarcerated? Yes ___ No __

Were you, or was anyone in your household in the hospital? Yes ___ No___

Were you, or was anyone in your household in any other type of institution?

Yes ___ No ___

If yes, were you in the institution when you noticed the infection? Y__ N___

Did you take antibiotics for any other reason? Yes ____ No ____

If yes, which antibiotic(s)? _____

In the month prior to your infection:

Did you have any outpatient surgery? Yes ___ No ___

Did you receive a piercing? Yes ___ No ____

Did you receive a tattoo? Yes ___ No ____

Do you have any ongoing health conditions (eczema or diabetes, e.g.?) Yes ____ No ____

If yes, please name: _____

Is anyone in your household, including yourself, a healthcare worker? Yes ___ No___

Do you know of anyone else who has or had symptoms similar to yours or who was diagnosed with MRSA recently? _____

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