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The molecular epidemiology of methicillin-resistant Staphylococcus aureus (MRSA) in the major countries of East Asia

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THE MOLECULAR EPIDEMIOLOGY OF METHICILLIN-RESISTANT
STAPHYLOCOCCUS AUREUS (MRSA) IN THE MAJOR COUNTRIES OF
EAST ASIA

by

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THE MOLECULAR EPIDEMIOLOGY OF METHICillin-RESISTANT
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ABSTRACT

Methicillin-resistant Staphylococcus aureus (MRSA) is a successful pathogen which was historically found in hospital settings but now is a common cause of infection in communities. The rapid emergence of community-acquired MRSA (CA-MRSA) at the turn of the 21st century has established this bacterium’s presence throughout the globe and MRSA continues to be endemic in certain countries. Asia is the most populous continent in the world and also holds a high burden of MRSA infection. This presents a concern for both public health and the acquisition of antibiotic resistance in this region. This literature review describes how MRSA became a successful pathogen. It provides a systematic review of the recent literature on MRSA in East Asia to identify major MRSA clones by country as determined by their molecular characteristics. Also to identify notable genetic and epidemiological factors associated with these MRSA clones.

The results of this review provided evidence of the importance of using molecular categorization techniques to accurately distinguish MRSA strains that require specific antibiotic treatment methods. It also provided evidence of CA-MRSA clones invading hospital settings and traditional hospital-acquired MRSA
(HA-MRSA) clones continuing to develop multi-drug resistance throughout East Asian countries. The results also detected novel MRSA strains across hospitals and reported the spread of major MRSA clones within and between countries. Strengthening existing surveillance systems and collaborative efforts between countries within Asia should be a priority to monitor the evolution and movement of MRSA especially in the age of globalization and accessible travel.
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**LIST OF ABBREVIATIONS**

ANSORP ................................. Asian Network for Surveillance of Resistant Pathogens  
CA-MRSA ............................... Community-acquired Methicillin-resistant *Staphylococcus aureus*  
CC ............................................................... Clonal Complex  
CDC ......................................................... Center for Disease Control  
DNA .......................................................... Deoxyribonucleic Acid  
HA-MRSA ................................. Hospital-acquired Methicillin-resistant *Staphylococcus aureus*  
HIV ......................................................... Human Immunodeficiency Virus  
MeSH ..................................................... Medical Subject Headings  
MIC ......................................................... Minimal Inhibitory Complex  
MLST ................................................. Multilocus Sequence Typing  
MRSA ............................................. Methicillin-resistant *Staphylococcus aureus*  
PFGE .................................................. Pulsed Field Gel Electrophoresis  
POT ...................................................... Phage Open-Reading Frame Typing  
PVL ..................................................... Panton-Valentine Leukocidin  
SCC*me*c .................................. Staphylococcal Cassette Chromosome *mec*  
ST ......................................................... Sequence Type  
WGS ..................................................... Whole Genome Sequencing  
WHO ................................................. World Health Organization
INTRODUCTION

History of *Staphylococcus aureus*

*Staphylococcus aureus* (*S. aureus*) is a gram-positive bacterium currently recognized as a major pathogen to humans due to its ubiquitous geographical distribution and rapid evolution documented in the early 21st century. *S. aureus* was first identified circulating within hospitals and now is a known cause for widespread infection in communities. Prior to discovery of antibiotics, *S. aureus* carried a high burden of morbidity and mortality where invasive bloodstream infections bore an 80% mortality rate [63]. The emergence of antibiotic resistance in *S. aureus* was identified only a few years after the introduction of penicillin in the 1940s [5]. In the 1960s, after the development of methicillin a semi-synthetic penicillin class antibiotic, another wave of resistance was reported from a hospital in the United Kingdom where methicillin-resistant *S. aureus* (MRSA) was first isolated. Soon after in the following two decades, reports of MRSA occurred throughout Europe and the United States [83]. During this time period, MRSA was acknowledged as a nosocomial pathogen causing serious infection in ill patients. However, reports of MRSA infection of community origin began to appear in the late 1990s with etiologies genetically unique to the isolates identified in healthcare settings [65]. These events coined the terms hospital-acquired MRSA (HA-MRSA) and community-acquired MRSA (CA-MRSA) to distinguish these new strains. CA-MRSA is known to typically manifest as and be the primary cause of skin and soft-tissue infections [20, 58]. Soon after its emergence, different lineages of CA-MRSA
were reported in the Americas, Europe, Africa, Asia and Oceania, establishing its presence at an international scale. Due to this pathogen’s rapid geographic dissemination and evolutionary trajectory, the Center for Disease Control and Prevention (CDC) in the United States and other similar entities around the world have recognized MRSA to be a major concern and threat to public health [2].

**Epidemiology of Community-Acquired MRSA**

Prior to the 1990s, infection with MRSA was thought to only occur in healthcare settings amongst at-risk groups that included the elderly, patients of invasive surgery or intravenous treatments, the chronically ill and those with comorbidities such as diabetes and HIV [20]. Other risk factors included previous hospital exposure, length of stay in hospitals and exposure to others infected with MRSA [65, 15]. The emergence of CA-MRSA was characterized by outbreaks in communities without contact to healthcare centers. This had led to many epidemiological studies investigating which populations are at high-risk and identifying risk factors for CA-MRSA infection. The first reports of MRSA infection in communities without traditional hospital risk factors associated with HA-MRSA occurred in Australia [13] and then in the United States during the late 1990s [20]. The following decade produced a large amount of literature identifying epidemiological determinants for CA-MRSA infection for the major strains primarily circulating in the United States and in Europe [74]. Unlike their nosocomial counterparts, CA-MRSA infection outbreaks occurred in both healthy children and
adults whom were seemingly low risk populations. Further outbreak investigations have identified CA-MRSA to disproportionally affect certain populations which include ethnic minority groups, infants, those of low socio-economic status, homeless populations, IV drug users, prisoners, men who have sex with men, athletes, emergency department patients, military personnel, indigenous populations and occupational livestock workers [14, 68, 83]. Additional host risk factors include those who are immunocompromised, diabetic, having cystic fibrosis and positive HIV status [83, 12]. Some of these studies alongside others have identified additional risk factors for CA-MRSA which include poor sanitation, crowding, shared equipment or hygienic products, settings with high risk for superficial skin wounds and lack of access to medical care [83]. Due to the epidemiological differences between HA- and CA-MRSA cases, the CDC proposed a CA-MRSA case definition dependent on the absence of certain epidemiological risk factors found in HA-MRSA and a temporal condition if a MRSA isolate is obtained within 48 hours of hospital admission [2]. Many studies categorizing cases in healthcare centers use this definition as an MRSA isolate obtained ≤48 hours after admission and HA-MRSA as an isolate obtained >48 hours after admission. All references to CA-MRSA and HA-MRSA in this literature review will be based on this definition unless specified. However, this definition has become less reliable due to the occurrence of HA-MRSA strains in the community and CA-MRSA emerging in healthcare settings, causing a blurring between these definitions [7, 47]. CA-MRSA clones have been reported to cause hospital
outbreaks in neonate units, newborns, post-operative patients, healthcare workers and their household members [14]. This leads to the emphasis of standardized methods and definitions for identifying strains of MRSA based on their molecular characteristics. The use of molecular typing is useful for identifying groupings of MRSA clones which can provide crucial information during an outbreak investigation or active nationwide surveillance.

**Molecular Typing Methods for MRSA**

To date, MRSA has been typically characterized by antibiotic susceptibility patterns and molecular typing by DNA fragment restriction profile pulsed-field gel electrophoresis (PFGE), select house-keeping genes by multilocus sequence typing (MLST), protein A (spa) typing, staphylococcal cassette chromosome mec (SCCmec) element typing, and the presence of virulence genes. It is important to note that molecular typing for MRSA has been pushing towards whole-genome sequencing (WGS) due to it’s high level of resolution and discrimination between strains [34]. Table 1 outlines general methods, advantages and examples of common nomenclature for the abovementioned MRSA molecular typing techniques in the order of discriminatory power from WGS to SCCmec. Early investigations have previously associated the carriage of Panton-Valentine Leukocidin (PVL) genes as a marker for CA-MRSA but further studies have identified that some community-acquired isolates do not contain PVL genes [81]. The identification of PVL has now only served to provide further resolution for
molecular classification and suggestive differences in clinical manifestations for MRSA infection [14].

WGS, as the name implies, involves the sequencing of genetic material in its entirety. This clearly gives this method the one of highest levels of resolution in discriminating between clones and strains but it is time-consuming and difficult to achieve in a clinically relevant time period. PFGE compares banding patterns of DNA fragments produced by restriction-enzyme digests and it is the “gold-standard” for outbreak investigations due to its ability to distinguish closely related strains. Despite the advantages of PFGE, it is technically difficult and time consuming. Also results of this method are also difficult to compare between laboratories and between different time periods. Notable examples of this classification based on the PFGE database from the United States are the major clones known as USA300, USA400, USA1000. Spa typing is based on sequencing polymorphisms in the spa gene that encodes the surface protein A (spa). It is cost-effective compared to PFGE and MLST with unambiguous data but misclassification of lineages can occur using this method. Spa typing currently uses two types of nomenclature systems, Ridom and eGenomics [66]. MLST is based on seven select house-keeping genes found throughout the genome where the fragments are sequenced and identified using a MLST database (http://saureus.mlst.net). Variations in each of the genes are considered to be alleles and are then combined to create unique profiles called sequence types (STs). It is important to note that there is a good level of congruence between
PFGE, spa typing and MLST [66]. Clonal Complexes (CC) are groups where STs share common allelic profiles. This method of categorization has been useful in grouping related clones using the eBURST program (http://eburst.mlst.net). It is typical to find variants of major STs within the same CC’s.

SCCmec typing classifies different SCCmec elements into one of eleven currently known types identified in the literature and stored in an online database (http://www.staphylococcus.net/) [62]. The most common molecular characterization method and nomenclature for MRSA is the use of SCCmec typing paired with ST to describe different clones with further resolution. This method has been useful to identify major clones of MRSA that have spread globally to various countries [58, 17]. Historically CA-MRSA strains have been differentiated from HA-MRSA strains based on SCCmec type [62]. CA-MRSA has been mainly associated with SCCmec type IV and occasionally with type V which both confer only beta-lactam resistance [14]. In comparison, HA-MRSA clones typically carry SCCmec types I, II, III containing additional multidrug resistance genes [52]. Turlej et al. provides a concise summary for the STs associated with SCCmec and the presence of resistance genes meca and ccr [78].
Table 1. Molecular characterization techniques for MRSA

This table displays each of the molecular characterization techniques used for MRSA in the order of resolution with whole-genome sequencing being the highest down to SCCmec typing. A brief description, advantages and limitations of each technique are described with an example of the nomenclature used for a predominant CA-MRSA clone in the United States known as USA300 or ST8-IV-t008. *spa typing by Ridom and eGenomics systems respectively.

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Advantages and Limitations</th>
<th>Example Nomenclature of CA-MRSA clone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole-genome sequencing [13]</td>
<td>Genome of the isolate is sequenced in it's entirety</td>
<td>Highest resolution for strain discrimination but time-consuming with high cost</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Pulsed-field gel electrophoresis [61]</td>
<td>Banding patterns of genomic DNA from isolates are compared to reference strains</td>
<td>High level of discriminative power between clones in short time periods but difficult inter-laboratory comparison</td>
<td>USA300</td>
</tr>
<tr>
<td>Protein A (spa) typing [53]</td>
<td>Amplification of spa and sequences are compared to online databases</td>
<td>Discriminatory power between MLST and PFGE</td>
<td>t008 or 1*</td>
</tr>
<tr>
<td>Multilocus sequence typing [16]</td>
<td>Fragments of house-keeping genes are sequenced to create an allelic profile</td>
<td>Analysis is unambiguous and advantageous grouping of clonal complexes, good for long-term evolution and clonal changes but time consuming</td>
<td>ST8</td>
</tr>
<tr>
<td>Staphylococcal cassette chromosome mec typing [78]</td>
<td>*mec and ccr genes are sequenced then genetic and structural characteristics are compared</td>
<td>Identification based on antibiotic resistance genes useful for epidemiological studies but time consuming and technically difficult</td>
<td>Type IV</td>
</tr>
</tbody>
</table>
Antibiotic Resistance of S. aureus

Penicillin was first introduced in the 1940s as a revolutionary treatment of previously fatal bacterial infections including S. aureus. However, after its discovery and use, resistance to penicillin in S. aureus quickly developed by the acquisition of a beta-lactamase. The second wave of resistance in S. aureus occurred only two years after methicillin was introduced in 1961 [5]. This is in comparison to vancomycin, a glycopeptide antibiotic first used in 1958, where resistance in S. aureus took almost 40 years to achieve [69]. The origins of methicillin resistance acquisition in S. aureus has been thought to have occurred through the horizontal transfer of the mecA resistance gene from another staphylococci species [77]. CA-MRSA clones tend to be susceptible to beta-lactam antibiotics, but increasing evidence of multi-drug resistance of CA-MRSA clones has led to concerns over available treatment options [18]. Resistance has been found in certain beta-lactams, glycopeptides, quinolones, aminoglycosides, fusidanes, macrolides and lincosamides. The susceptibility of MRSA isolates is typically determined by evaluating the minimal inhibitory concentration (MIC), which is the minimal concentration of an antibiotic necessary to inhibit the growth of the MRSA isolate. The summary of resistance rates for various antibiotics gives a unique antibiotic resistance profile to tested isolates.

Different STs and SCCmec types have been known to contain distinct resistance profiles. MRSA strains that are traditionally hospital-acquired and contained SCCmec types II and III typically have resistance to multiple antibiotics.
CA-MRSA strains which are classically SCCmec types IV and V tend to be susceptible to more antibiotics. Chua et al. provides the antibiotic profiles for resistance by ST, SCCmec type and PVL status for major global clones of MRSA [9]. Resistance patterns differ by major clones throughout the world, within continents and even within countries there is heterogeneity for resistance profiles. Potential for increased resistance is always a threat which requires the active development of new antibiotics and appropriate usage of existing antibiotics to prevent the development of further resistance.

**Carriage and Clinical Symptoms of CA-MRSA**

*S. aureus* is the most commonly isolated agent in skin and soft tissue infections and has been the causative agent of clinical symptoms which range from self-limiting to severe in nature. There are high rates of colonization of *S. aureus* in people with common sites occurring in the nares, throat, axilla, groin, breast, hands, neck and rectal region [15]. Carriers of CA-MRSA have a higher risk of infection compared to those without colonization and also serve as a reservoir for the spread of MRSA in communities [14]. CA-MRSA has been associated with skin and soft tissue infection with clinical presentations of abscesses and cellulitis being most common. Other manifestations include erysipelas, folliculitis, impetigo, lymphadenitis, carbuncles, and furuncles. Some strains have been identified to cause severe and invasive disease such as necrotizing fasciitis, osteomyelitis, pneumonia, endocarditis, sepsis, myositis, and pyomyositis [28, 14].
Major International CA-MRSA Clones

Since the first reported case of CA-MRSA, unique genotypes of CA-MRSA began to rapidly appear across each continent. Some of these CA-MRSA clones were geographically limited to their location of origin while other “international” clones were successful in causing outbreaks in distant locations far from where they first isolated. MLST and SCC\textit{mec} typing have established only a few major international clones and their closely related genetic variants.

Table 2 contains the predominant CA-MRSA clones in various world regions by ST and SCC\textit{mec} types. The major CA-MRSA clones that have been identified in the literature include ST1-IV, ST8-IV, ST30-IV and ST59-V. Despite not being the dominant clones in all continents, ST8-IV and ST30-IV are considered to be truly global clones as they are the only clones that have been isolated from all continents except for Antarctica [45].

CA-MRSA has been well documented in the United States since the first outbreak in the Midwest from 1997-1999 [3]. During the time period before 2001, the ST1-IV strain or USA400 was the most prevalent CA-MRSA strains. However, a shift occurred to ST8-IV with PVL genes or USA300 becoming the predominant strain and leading cause of all community-acquired bacterial infections in the United States [44]. USA300 has continued in its geographical spread to Canada and has also been isolated in Europe, the Middle East, Asia, Africa and Oceania [50, 51].
Europe’s predominant CA-MRSA clone is ST80-IV, which has been isolated in Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Netherlands, Norway, Poland, Romania, Spain, Slovenia, Sweden, and Switzerland [55, 60]. There is a high level of genetic heterogeneity of CA-MRSA despite it’s lower prevalence compared to the United States [67]. There is evidence that ST80-IV may have originated from northern Africa before becoming the most widely distributed CA-MRSA clone in Europe [67].

In South America, there have been limited studies on the molecular epidemiology of CA-MRSA, but regional differences in predominant strains have been identified. ST5-IV has been identified as the major clone in the northern portion of South America and Argentina [64]. MRSA in Brazil has been characterized by HA-MRSA strains’ proliferation into communities, while a non-multidrug resistant CA-MRSA isolates are being found in hospital settings [59].

Similar to South America there is limited data on the molecular characteristics of CA-MRSA in Africa. ST88 with SCCmec types III and V (ST88-III/V) are the major MRSA clones throughout all regions of Africa except for northern Africa where ST80-IV is the predominant clone. ST88-III/V is rarely found elsewhere in the world except for South East Asia [1].

Isolates in Asia also contain a wide range of genetic diversity relative to the United States. However, the ST59 clone has established itself in multiple countries. In Taiwan, the majority of isolates are of ST59 [45]. ST59 in China is not as prevalent compared to Taiwan. Most Asian CA-MRSA isolates do not carry PVL
genes with the exception of known imported cases. This is true in South Korea where ST89 and ST8 without PVL genes are the major clones. CA-MRSA in Japan is molecularly diverse but cases of both multidrug resistant USA300 and imported USA300 have been reported. ST59-V with PVL genes from Taiwan has also been established in Japan since 2010 [10].

Australia has two major CA-MRSA clones, ST93-IV and ST30-IV. ST93-IV has become the predominant clone since 2008 and it has been linked to both skin and invasive infections. ST30-IV originated from New Zealand where it was the predominant clone until 2005, after which ST5-IV became dominant. Despite this ST30-IV has successful spread to North America and Europe [85].

Table 2. Major CA-MRSA Clones in the World

This table lists the major CA-MRSA clones from each region in the world. The clones listed are predominant clones based on literature reviews for each region [1, 44, 45, 64, 67, 85].

<table>
<thead>
<tr>
<th>Region</th>
<th>Major CA-MRSA Clones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>ST59-IV/V</td>
</tr>
<tr>
<td>North America</td>
<td>ST8-IV, ST1-IV</td>
</tr>
<tr>
<td>Europe</td>
<td>ST80-IV, ST398-IV/V</td>
</tr>
<tr>
<td>Oceania</td>
<td>ST1-IV, ST30-IV, ST93-IV</td>
</tr>
<tr>
<td>Africa</td>
<td>ST88-III/V, ST80-IV</td>
</tr>
<tr>
<td>South America</td>
<td>ST5-IV</td>
</tr>
</tbody>
</table>
OBJECTIVES AND METHODS

The World Health Organization (WHO) has emphasized initiatives to combat the developing threat of antimicrobial resistance to both local and global public health [84]. The continent of Asia in recent years has been identified to be a hotspot for antimicrobial resistance [29, 27]. The rapid emergence and success of CA-MRSA strains has demonstrated the pandemic capabilities of a seemingly treatable pathogen. In Asia, MRSA is unique by its high prevalence relative to other continents and wide genetic diversity between and within countries [25]. The ways that *S. aureus* has already adapted virulence and resistance genes is of concern especially in environments that may continue to promote the pathogen’s evolution in obtaining antibiotic resistance. The blurring of CA-MRSA and HA-MRSA, by the presence of community strains in the hospital setting and vice-versa also stresses the need for constant molecular evaluation of these strains. The objective of this library thesis is to provide a brief overview of recent literature on the molecular epidemiology of MRSA in the major East Asian countries, to identify major MRSA clones by their genetic characteristics and to characterize the antibiotic profiles of these clones. Using molecular epidemiology to identify changes in major MRSA clones serves to make informed clinical and public health decisions.

This literature review was conducted by searching for observational studies and reports on MRSA infection and colonization in East Asia. China, Hong Kong, Japan, Mongolia, South Korea and Taiwan were chosen for study as they are the major East Asian countries, based on the United Nations Statistical Division's
definition of East Asia [80]. PubMed searches were conducted with the following criteria using the MeSH terms “Molecular Epidemiology”[Mesh], “Methicillin-Resistant Staphylococcus aureus”[Mesh], and “Far East”[Mesh]. The time frame for the literature review was within the past 6 years. Additional exclusion criteria for the studies were as follows: if a study did not include any one of the genotyping techniques: PFGE, MLST and SCCmec typing [12], if the articles were not published in English, or if articles lacked appropriate translations of the manuscripts. The combined MeSH terms used were as follows: ("Molecular Epidemiology”[Mesh] AND "Methicillin-Resistant Staphylococcus aureus”[Mesh]) AND "Far East”[Mesh] AND ("2010/01/01"[PDAT] : "2016/10/15"[PDAT])
Figure 1: Major Countries of the Far East Geographic map

This figure displays the major countries of the Far East that were included in this library thesis. China in blue, Taiwan in green, South Korea in orange, Japan in purple and Hong Kong in red. ArcGIS Pro was used to create the map (ESRI 2016. ArcGIS Pro Desktop: Release 1.1. Redlands, CA: Environmental Systems Research Institute, Inc.) using country boundary shapefiles provided by GADM | Boundaries without limits (http://www.gadm.org/).
RESULTS AND DISCUSSION

Based on the MeSH terms and exclusion criteria, 26 primary literature articles of human observational studies and reports with relevant molecular epidemiology information of CA-MRSA were found. These investigations were conducted in China, Hong Kong, Japan, South Korea, and Hong Kong, while there was none for Mongolia. The distribution of the articles by country is as follows: 9 from China, 1 from Hong Kong, 6 from Japan, 3 from South Korea and 7 from Taiwan. Twenty-two studies examined samples from hospitals while two studies were conducted in nursing homes and one in a child daycare center. Of the 26 studies, six considered colonization of MRSA for their investigations while the remainder were based on only MRSA infection. 23 studies tested for antimicrobial susceptibility. All 26 studies used SCCmec for molecular characterization of MRSA isolates, while 22 studies also used MLST and half also used PFGE and spa typing. Approximately on average three of the four listed molecular characterization techniques were used in each study. 19 studies specified the sites where samples for S. aureus isolates were taken. Skin and blood were the most common sample sites for MRSA isolates and multiple sampling sites were used in 13 studies. A unique note is that one study investigated the molecular epidemiology of MRSA isolates from ocular infection.
MOLECULAR EPIDEMIOLOGY

China

Of the 9 results from the literature search in China, 8 studies in China which were conducted in hospital settings primarily focusing on MRSA infection. ST239-III has been reported to be the dominant hospital-associated clone in China since the 1990s [7]. This clone along with ST5-II were the most commonly isolated clones (Table 3) Cheng H et al. investigated the characteristics of these two predominant clones from teaching hospitals found in six cities across the country [8]. Samples were taken from January 2009 to March 2012 from patients. There was an average 59.8% prevalence of MRSA in all isolates. Interestingly there was higher prevalence in hospitals found in coastal cities compared to hospitals in cities located further inland. The most common SCCmec type was III constituting 57.6% of all isolates, and it was followed by SCCmec II and IV which represented 22% and 8% respectively. From MLST, 15 STs were identified including 4 new STs. This study suggests a wide distribution of these major clones in China due to their prevalence in multiple hospitals across the entire country. Tian et al. also reported ST239-III and ST5-II from MRSA isolates collected during 2002 to 2008 from three hospitals in Shenyang, China which is geographically adjacent to the Korean peninsula [75]. ST239-III was found in higher prevalence than the ST5-II clone. The predominance of ST239-III was also seen in the study by Xiao et al. where HA-MRSA isolates were obtained in the first 6 months of 2011 from 69 hospitals from 45 large cities for nationwide surveillance in China [86]. Based on the 1,141
MRSA isolates, over 30 STs were identified with ST239-III being the most common followed by ST5-II and ST59-IV. Xie et al. confirmed the predominant distribution of ST239-III based on a study from southern Guangzhou province [87]. Based on inpatient MRSA samples from 2006 to 2011, 12 STs were identified with ST239-III being the most prevalent. This study also compared clinical demographic information and clinical symptoms between HA-MRSA and CA-MRSA infection [87]. This study reported variability in PVL genes across both HA-MRSA and CA-MRSA isolates suggesting that PVL is not a reliable molecular indicator to identify CA-MRSA from HA-MRSA in China. This is similar to a multisite healthcare study reported the variability in PVL genes from isolates was seen between PFGE pulsotypes [40]. Also Yao et al. reported high prevalence of PVL genes in both HA-MRSA and CA-MRSA isolates in China [88].

Yao et al. investigated the molecular epidemiology of MRSA isolates from skin and soft tissue infections, a common clinical manifestation of CA-MRSA, at a teaching hospital from December 2002 to June 2008 [88]. 54% of skin and soft tissue infection isolates were MRSA. 66.7% of the MRSA isolates were hospital-associated based on the CDC definition mentioned earlier. ST239-III was the predominant ST in both HA- and CA-MRSA isolates with ST5-II being second most prevalent. SCCmec types III and IV were the most commonly found in HA- and CA-MRSA isolates respectively. The blurring of the CDC definition of hospitals versus community acquired infection is seen in this study. Despite skin and soft tissue infections being the major clinical manifestation of CA-MRSA, ST239-III a
HA-MRSA clone was identified to be the predominant clone causing these infections in this study. This gives evidence of HA-MRSA clones causing clinical symptoms typically associated with CA-MRSA clones while ST239-III still remains to the predominant clone in hospitals across China. Despite the predominance of ST239-III and ST5-II throughout Chinese hospitals, Li J et al. identified ST59-IV and ST59-V to be the dominant clones from isolates taken from pediatric and university hospitals across China from 2005 to 2011 [39]. This study was the first to report CA-MRSA strains belonging to the same clonal cluster, CC59, in children from Chinese hospitals. Li S et al. also investigated the prevalence of virulence genes in child patients in four regional hospitals from 2004 to 2012 [40]. Isolates were taken from multiple sites which identified 22 STs of which ST59-IV (35.8%) was the most prevalent followed by ST239-III (22.6%). This provides further support that the ST59 MRSA clone is invading hospital centers.

The major hospital-associated clones in China are still of concern due to their recognized broad range of antibiotic resistance associated with SCCmec types I, II and III. Zhang H et al. conducted a multi-center study of MRSA skin infections to compare the molecular characteristics of isolates to their susceptibility to ceftaroline, a newly developed cephalosporin [89]. HA-MRSA samples were taken from 56 hospitals during the same time period as the nationwide study done by Xiao et al. [86]. Based on these isolates, they determined that the majority of non-susceptible isolates belonged to a single clonal cluster and that ST239-III contributed to the majority of ceftaroline resistant isolates. There was also
evidence of continued evolution based on clones with single nucleotide mutations in ST239-III within the same clonal complex.

The overlap of HA-MRSA and CA-MRSA clones in other settings outside of hospitals was also seen in study by Zhang J et al. of MRSA colonization in multiple nursing homes within Shanghai [90]. Samples were taken over a one-month period in 2014. The overall prevalence of MRSA was 10.6% and 18 different STs were identified. The predominant ST differed between sampling sites where ST1 was the most common for nasal swabs, axillary samples were both ST1 and ST398, and ST398 for skin samples. This study demonstrated that a single individual can be colonized with multiple strains in different body sites which has important implications for screening and elimination of MRSA for patients. Nursing homes are an interesting intersection between the community and healthcare settings where the distribution and sources of CA-MRSA and HA-MRSA require further investigation.

The studies of MRSA in China demonstrate the wide range of genotypic diversity in the country, not only within individual healthcare centers but across the country in different regions. The identification of novel STs is also notable as Yao et al. reported 3 novel STs over a 6-year period from a single teaching hospital [88]. Cheng et al. and Xiao et al. both conducted studies from multiple hospitals in different regions and reported 4 and 15 novel STs respectively [51, 88]. From the 15 novel STs Xiao et al. reported a single novel ST occurring in two different
hospitals in the middle and eastern regions of China suggesting that the dissemination of novel clones can occur over large areas [86].

**Taiwan and Hong Kong**

MRSA has been heavily studied in Taiwan compared to other East Asian countries. HA-MRSA have been reported since the early 1990s with ST254-IV and ST239-III being the two major clones [7]. Entering the 2000s, ST239-III became the predominant clone and it has disseminated throughout the country. Kuo et al. compared the molecular characteristics of patients presenting with bacteremia due to CA-MRSA by SCCmec type between 2004 to 2008 in a tertiary healthcare center [35]. ST239-III was the most common clone among SCCmec type I while ST59 was the most common for SCCmec types II, IV, and V. However, recent evidence shows a decrease of ST239-III with an increased prevalence of ST5-II, a clone with a known international presence, and ST59-IV [7]. ST5-II is a HA-MRSA clone first reported in 2006 from a respiratory care ward outbreak in Central Taiwan [38]. All the studies in Taiwan from this literature review reported the presence of ST59-IV in isolates taken from hospitals, nursing homes and day cares throughout Taiwan. Similar to China, the invasion of traditional CA-MRSA into healthcare settings is seen with the presence of ST59-IV in epidemiologically defined HA-MRSA infections. Ho et al. analyzed isolates from blood samples taken from patients in a university hospital over a five-month period in 2008 [21]. ST5-II and ST239-III were the predominant clones with ST59-IV/V being the third most prevalent clone. Despite the decreasing predominance of ST239-III in Taiwan, this
clone is still of concern as Lin et al. reported intermediate levels of resistance to vancomycin (MIC between 4 to 8 µg/ml) during 2009 in a teaching hospital [41]. Based on 118 patients, a 4.2% prevalence of vancomycin resistance in all S. aureus isolates and 8.1% vancomycin resistance in MRSA isolates were reported. In the vancomycin resistant isolates, five different PFGE pulsotypes were found, each unique to the five patients. MLST determined ST239-III and its single locus variant to be the predominant clones from the four of the five patients while the other isolate was ST5-II. This is the highest rate of vancomycin resistant S. aureus in Taiwan but it is lower compared to a multi-city study in China (13.1%) [70].

Earlier, from 2001 to 2002, Hsueh et al. identified the expansion of a single pulsotype with SCCmec type III from 21 patients in Taipei teaching hospital [24]. This investigation demonstrated the ability of a single clone with intermediate vancomycin resistance to spread within a healthcare facility. The results from this study emphasize the selective pressure of antibiotic use and indicate the importance of proper antibiotic treatment in preventing the emergence of antibiotic resistant clones. The development of vancomycin resistance in ST239-III major clone and evidence of clonal spread in Taiwan demands for increased monitoring and molecular surveillance to prevent the expansion of a vancomycin resistant outbreak or epidemic.

The importance of MRSA infection control was seen in the outbreak investigation in 2006 within a Taiwanese respiratory care ward [38]. The spread of a single dominant clone in this respiratory ward demonstrated the potential of
transmission between patients and healthcare workers in a hospital setting. Samples taken from both patients and healthcare workers identified ST5-II as the most commonly isolated clone in both groups. This was the first report of ST5-II in Taiwan, although it was a common HA-MRSA clone in Japan and South Korea prior to 2006 [33]. This outbreak was also the first to report ST45-V in Taiwan, originating from Europe [14]. It is an interesting note that Tsao et al. reported this specific strain from colonization swabs taken from residents and staff during the summer of 2012 across 14 nursing homes [76]. The majority of SCCmec types in this study were IV and V (71.4%) compared to the less common SCCmec types II and III (8.4%). ST45-IV/V (30%) was most common followed by ST30-IV (12%) and ST239-III (5%). There is previous literature on the spread of ST45 throughout nursing homes in Taiwan and China [23]. The relationship with ST45 transition into being prevalent in nursing homes from a hospital origin requires further investigation. There is evidence of increased carriage in nursing residents after an acute medical event in a hospital and many have been identified to be HA-MRSA clones, in particular ST239-III. The transport of MRSA colonization through these transitions may have implications for appropriate screening of new residents for infection control purposes.

Sampling sites for MRSA are typically from blood, skin, nasal, drainage from infection sites, and other bodily fluids. Kang et al. presents a unique study on characterizing the molecular epidemiology of MRSA from ocular sites [30]. Conducted from 2010 to 2011, 59 patients were identified with S. aureus with 34
of them being MRSA. The most common clone was ST59-IV/V which is the most common CA-MRSA clone in Taiwan. The second most common clone was ST239-III, historically found in the hospital setting. This demonstrates consistency with the distribution of HA- and CA-MRSA clones from non-ocular sites based on epidemiological definitions.

The results of this the literature search found one study based in Hong Kong investigated risk factors associated with colonization of MRSA in children among day care and kindergarten centers [22]. This large scale study across 79 daycare centers and 113 kindergarten centers obtained samples during the academic year from 2009 to 2010. The carriage of MRSA was similar between day care centers and kindergarten centers with a 1.3% prevalence. ST59 carrying SCCmec types IV and V were most common followed by ST45 also with SCCmec types IV and V. The isolates were genetically diverse and included strains of ST10-V and ST1-IV. This was the first report of ST1-IV in Hong Kong. ST10-V is novel MRSA genotype while ST1-IV has been found across the world in the United States, Europe and Asia [57].
South Korea and Japan

South Korea has been known to have a high burden of MRSA (>70%) compared to other countries in Asia [46,66]. ST5-II, ST239-III, and ST72-IV were the most prevalent clones isolated in the three studies from the literature search shown in Table 3. ST5-II and ST239-III have been established to be predominant clones in South Korean hospitals since the mid 1990s [4]. Kim et al. analyzed randomized stored samples from patients in hospitals and nasal swabs from healthy individuals over a prolonged period from 1996 to 2005 [32]. ST5-II and ST239-III were the most prevalent clones during the study period in both clinical and community isolates. It is notable that from community sampling in the years of 1997-1998 and 2005 the nasal carriage prevalence of MRSA increased from 0% to 8% and ST72-IV emerged to be the most common ST for CA-MRSA. This predominant CA-MRSA clone is unique due to the lack of PVL genes; a feature that is geographically unique to South Korea. CA-MRSA ST72 clones typically contain PVL genes are found in North America and Europe [7, 25]. Despite being primarily isolated as a community-associated clone there is recent evidence of ST72 invasion into healthcare settings [56]. This was evident in a study by Kwon et al. where analyzing MRSA bacteremia isolates and nasal swabs across 10 intensive care units [36]. This group used a different set of definitions compared to the CDC, where imported cases were within 72 hours after admission and acquired cases was defined as at or more than 72 hours after admission. Seven PFGE pulsotypes had the same MLST profile of ST5-II (61.9%) One PFGE pulsotype
consisted of all ST72-IV which was 22.5% of all isolates and was the dominant ST in hospital-associated cases. Sung et al. investigated MRSA bacteremia among pediatric patients in two tertiary hospitals [71]. During the study period from 2006 to 2010 ST72-IV was most common in both CA-MRSA isolates (62.5%) and HA-MRSA isolates (41%) from pediatric wards. Other strains identified in this study were ST89-II, ST239-II/III and a ST239-III single locus variant. There was a low prevalence of PVL genes in CA-MRSA isolates while there was no carriage of PVL genes in HA-MRSA isolates. The authors previous study suggests that ST72-IV is the predominant clone among healthy South Korean children [37]. A notable genotype from this study is ST8-IV (a.k.a. USA300) which is the predominant clone from the United States. International spread of this strain was not detected in previous South Korean pediatric colonization studies [37]. ST89, a predominant Japanese clone, was also identified in this previous study. Sung et al. reported a diverse range of STs including one novel ST and several single locus variants.

In Japan, the major clones identified from this literature review were ST5-II and ST8-IV with a variety of minor clones shown in Table 3. ST30-IV and ST30-I were the predominant clones from hospital settings in Japan until ST5-II became the dominant clone during the 1990s [42]. This shift was speculated to have occurred due the extensive used of antibiotics throughout Japan in the 1980s allowing the SCCmec type II, which harbors more multi-resistance genes, to influence which MRSA strains would be successful. ST8-IV is also known to be a prevalent CA-MRSA clone in the United States and Europe but has been relatively
rare in Japan aside from imported cases associated with small outbreaks [25]. The ST8 strains that have been identified in Japan typically do not carry the PVL genes compared to their USA counterparts. Taguchi et al. conducted an analysis on CA-MRSA from a small adult inpatient cohort admitted into a university hospital in Tokyo from 2008 to 2009 [72]. This is the first report of CA-MRSA strains found in critically ill inpatients from Japan. Based on genotyping HA-MRSA strains of ST5-II contained PVL genes and the CA-MRSA strains contained PVL genes and were SCC{	extit{mec}} type IV. However, small sample size and study population limits generalizability to only suggest importance of detecting the presence of PVL genes from critically ill patients in Japan.

ST5-II was the predominant clone found in the studies conducted by Otsuka et al. [54] and Inomata et al. [26]. Inomata et al. analyzed isolates from outpatients in a tertiary hospital from 2012 to 2013. The majority of isolates taken from multiple body sites were HA-MRSA. A notable finding in this study was the first report of ST5-IV in Japan. ST5-IV is a major pandemic clone that has been typically detected in the United States, countries in South American, and most recently, in South Korea [4, 6]. The presence of an emergent pandemic clone requires further analysis of it’s specific microbiology to understand it’s prevalence in Japan. Otsuka et al. investigated the MRSA genotypes in children on Sado Island [54]. Sado Island is considered to be an area of low antibiotic pressure due to it’s low rates of antibiotic use, geographic isolation, and lack of movement of individuals between the main island of Japan. Isolates were taken from pediatric outpatients and at
checkups for healthy individuals through an island-wide surveillance program. Nine STs were reported with ST5-II, ST8-IV, and ST764-II constituting the majority. A novel single locus variant of a ST1 strain was also isolated in this study. The results provide evidence of HA-MRSA clones appearing in communities outside of healthcare settings in low antibiotic pressure environments. ST764-II is a single locus variant of ST5-II first identified in Niigata, Japan from 2005 to 2009 [73]. The proximity of Sado Island to Niigata may explain the prevalence of ST764-II among both healthy and outpatient children. Nakaminami et al. reported ST764-II as the predominant clone followed by ST5-II in isolates taken from four tertiary hospitals in Tokyo during 2009 [49]. However, the ST764-II isolated in this study was a novel clone with different virulence genes from the clones identified in Niigata [31] and Hokkaido [73]. This provides evidence of the spread of a novel strain throughout various health centers in Tokyo and similarity in the emergence of novel clones between different regions within Japan.

Regional differences in MSRA strains within Japan is further shown by an investigation on the southern island of Okinawa from 2008 to 2010 by Mine et al. [48]. Samples taken from skin and soft tissue infections of outpatients in clinics and hospitals across Okinawa had a prevalence of 36.1% for MRSA, where 6.2% contained PVL genes. Only isolates that contained PVL genes were subjected to MLST which identified ST8-IV to be the most common among PVL-positive strains. This points to the recent emergence and spread of PVL-positive ST8-IV clones in Japan. The authors suggest that the high prevalence of strains with PVL genes
may be related to the large number of United States military bases on Okinawa. Military personnel and groups living in closed quarters such as military barracks are known to be at risk for CA-MRSA infection with clones such as ST8-IV with PVL genes [14]. Urehara et al. provided a short report on familial MRSA infection from a pediatric hospital in Tokyo [79]. Molecular analysis of the isolates from 8 child and 2 parent cases displayed each family contained a unique strain, suggesting the potential transmission of MRSA among family members. ST8-IV was found in three families, ST858-IV a single locus variant of ST8 in another family, and ST30-IV in a third family. ST30-IV had been a prevalent HA-MRSA clone in Japan since the 1980s. However, a shift of spa type, t021 to t019 within the endemic ST30-IV Japanese clone resulted in this HA-MRSA clone emerging within communities [25]. Urehara et al. provides evidence of risk factors for the transmission of CA-MRSA, including close contact and sharing of bathing products within families [79]. Suggested transmission prevention methods between family members would include hygienic education and proper hygienic practices.
Table 3. MRSA Clones Study Results by Country

The table shows the predominant and minor clones in the major East Asian countries based on the order of prevalence within each study. Notable strains included newly emergent strains in the country and novel STs are any strains identified in the study that did not exist in the MLST database (http://saureus.mlst.net/). Studies from the literature search that did not utilize MLST in their molecular analysis were excluded from this table. *All studies listed were based on MRSA infection with the exception of Zhang J et al. [90], Kang et al. [30] and Tsao et al. [76] which investigated carriage or colonization of MRSA.

<table>
<thead>
<tr>
<th>Country</th>
<th>Study</th>
<th>Predominant Clones</th>
<th>Minor Clones</th>
<th>Notable</th>
</tr>
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<td>ST5-II</td>
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<td>ST59-IV/V</td>
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<td>ST59-IV/V</td>
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<td>ST59-IV/V</td>
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<td>ST59-IV/V</td>
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<td>Li et al. (2014)</td>
<td>ST59-IV</td>
<td>ST59-IV/V</td>
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<tr>
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<td>Zhang H et al. (2015)</td>
<td>ST1-I/IV</td>
<td>ST398-V</td>
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<td>ST59-IV/V</td>
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<td>ST59-IV/V</td>
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<td>Kang et al. (2015)*</td>
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<td>1 novel</td>
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ANTIBIOTIC RESISTANCE PROFILES

China

From the studies based in China included in this literature review ciprofloxacin, clindamycin, erythromycin, gentamicin, rifampicin, trimethoprim-sulfamethoxazole and vancomycin were the most commonly tested drugs for assessing MRSA isolate susceptibility (in Table 4). The majority of studies were conducted in hospitals and the samples contain varying proportions of genetically unique CA- and HA-MRSA isolates which do not allow direct comparison of the resistance rates between studies. Not all the studies provided information on whether the investigators stratified the resistance rates by molecularly defined differences, such as ST or SCCmec type for comparison. The studies based in China demonstrated there is high variability of resistance rates in isolates from different body sites, various STs and SCCmec types, and between community-associated and hospital-associated MRSA clones.

The known differences for antibiotic resistance profiles between SCCmec types II and III versus IV and V (as mentioned earlier), were consistent across the studies by Cheng et al. [8], Li et al. [39], Xiao et al. [86], and Xie et al. [87]. The study by Cheng et al. showed generally high rates of resistance for all isolates [8]. SCCmec types II and III shared the same antibiotic resistance profile with resistance rates above 70% for non-beta lactam antibiotics; gentamicin, ciprofloxacin, clindamycin, erythromycin, tetracycline, levofloxacin, trimethoprim-sulfamethoxazole. SCCmec types I and V showed high rates of resistance to three
non-beta lactam antibiotics; clindamycin, erythromycin and levofloxacin. ST239-III and ST5-II shared the same resistance profile and most isolates of these clones were resistant to clindamycin, tetracycline and trimethoprim-sulfamethoxazole. Similarly, Tian et al. found that isolates with ST239 and ST5 (HA-MRSA strains), were resistant to multiple antibiotics (erythromycin, ciprofloxacin, levofloxacin, clindamycin and gentamycin). ST59, an emerging CA-MRSA strain, was susceptible to the same antibiotics as ST239 and ST5 with the addition of ciprofloxacin, levofloxacin and gentamicin but highly resistant to erythromycin and clindamycin [75]. Xie et al. reported that HA-MRSA isolates had significantly higher rates of resistance compared to CA-MRSA isolates for ciprofloxacin, moxifloxacin, rifampicin, clindamycin, tetracycline [87]. All isolates were susceptible to vancomycin, teicoplanin and linezolid.

Xiao et al. found that resistance varied even within different spa types of ST defined strains [86]. All ST239-III-t030 were resistant to ciprofloxacin and rifampin. However, susceptibility to trimethoprim-sulfamethoxazole demonstrated only 8.2% of ST239-III-t037 isolates with the same resistance patterns. ST5-II isolates were more likely to be resistant to ciprofloxacin. The majority of ST59-IV isolates were susceptible to ciprofloxacin, rifampin and trimethoprim-sulfamethoxazole. In the study by Li et al. the variability of resistance profiles was also seen between isolates containing the sasX virulence gene [40]. The rates of resistance for ST239-III with sasX genes for clindamycin, ciprofloxacin, erythromycin, trimethoprim-sulfamethoxazole were significantly higher compared to isolates.
without the sasX gene. This demonstrates the high variability of antibiotic resistance profiles even within the same sequence types. None of the isolates were resistant to vancomycin. Differences in resistance was also seen between PFGE pulsotypes where Li et al. identified significant differences in chloramphenicol resistance and differences in chloramphenicol and ciprofloxacin resistance in the ST59 SCCmech types IV and V [39].

When examining different sites of colonization Zhang J et al. identified that patterns of resistance were similar for most antibiotics across nasal, axillary and skin sites [90]. However, there were differences with certain antibiotics with gentamicin having lower resistance in nasal isolates compared to other sites and lower tetracycline resistance in skin isolates.

There is concern of major clones developing resistance to new drugs with the implication of limiting treatment options or selective pressure. Zhang H et al. investigated MRSA susceptibility to ceftaroline, a newer cephalosporin in isolates across China [89]. ST239-III, a major HA-MRSA in China, was responsible for the majority of ceftaroline resistant isolates. Despite these concerns, these strains were still susceptible to vancomycin, norvancomycin, linezolid and teicoplanin. All the studies in this review demonstrated that vancomycin resistance (MIC >2ug/ml) was not detected in any isolates. However, it is known that China does have evidence of high vancomycin resistance rates which were not captured in this literature review [70].
Table 4. Overall antibiotic resistance rates for studies in China

The table lists all the antibiotics tested for resistance and provides the overall resistance rate (%) for each study in China. The percentages represent the resistance rate in all samples from each study which contain combinations of CA-MRSA and HA-MRSA isolates. Xiao et al. [86] was not included as the authors did not provide drug specific resistance rates.

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Taiwan and Hong Kong

Within Taiwan and Hong Kong the resistant profiles among MRSA clones were unique in their molecular characteristics. The most common antibiotics tested for MRSA resistance were ciprofloxacin, clindamycin, erythromycin, gentamicin, trimethoprim-sulfamethoxazole, and vancomycin (Table 5). Differences in resistance rates between SCCmec types II and III to SCCmec types IV and V were seen in multiple studies. Lee et al. found that patients and healthcare workers with SCCmec types IV and V were resistance to fewer antibiotics compared to those infected with SCCmec types II and III [38]. The antibiotic profiles for the SCCmec types II and III in this study were almost all identical. Kuo et al. showed SCCmec types II and III to be more resistant to ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, and vancomycin compared to other SCCmec types [35]. SCCmec type III had the highest rate of resistance to vancomycin compared to other SCCmec types II, IV and V. Isolates with SCCmec types IV and V were more susceptible to gentamicin but higher resistance to rifampicin compared to SCCmec II and III. The same study also reported high rates of resistance to linezolid, tigecycline, and daptomycin across all isolates [25]. Kang et al., when investigating ocular samples found that all SCCmec type IV and V were completely or highly susceptible to all antibiotics except for clindamycin, erythromycin, cefoxitin, and penicillin [30]. The HA-MRSA with SCCmec types I, II and III had significantly higher rates of resistance except for vancomycin, and teicoplanin where no resistance was seen to these two antibiotics. The distinction between HA- and CA-
MRSA associated SCCmec types was also seen in isolates taken from nursing homes. Tsao et al. reported that MRSA isolates carrying the same SCCmec type had similar antimicrobial susceptibility patterns [76]. MRSA isolates with SCCmec III were multi-resistant to erythromycin, ciprofloxacin, trimethoprim–sulfamethoxazole, and clindamycin. In this study all isolates were susceptible to linezolid, vancomycin, and teicoplanin. From all the studies in Taiwan, only Kuo et al. [35] and Lin et al. [41] reported intermediate vancomycin resistance in a low proportion of their isolates.

In Hong Kong, Ho PL et al. found that 60.7% of MRSA isolates were resistant to erythromycin, 60.6% to clindamycin, 17.9% to gentamicin, 32.1% to tetracycline, 14.3% to chloramphenicol, and 25% to ciprofloxacin [22]. ST59-IV/V isolates were resistant to chloramphenicol, erythromycin, and tetracycline. ST45-IV/V isolates were resistant to ciprofloxacin erythromycin, gentamicin, and tetracycline. Trimethoprim-sulfamethoxazole, minocycline, fusidic acid, and rifampicin were active against all isolates in this study [22].
Table 5. Overall antibiotic resistance rates for studies in Taiwan and Hong Kong

The table lists all the antibiotics tested for resistance and provides the overall resistance rate (%) for each study in Taiwan and Hong Kong*. The percentages represent the resistance rate in all samples from each study which contain combinations of CA-MRSA and HA-MRSA isolates. Different MIC cut-offs were reported† when testing vancomycin resistance, Kuo et al. [35] used >1ug/mL and Lin et al. [41] used 2ug/mL.

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South Korea and Japan

For South Korea and Japan, the most commonly tested antibiotics were clindamycin, erythromycin, gentamicin, trimethoprim-sulfamethoxazole, and vancomycin (Table 6). In South Korea unique antibiotic resistance profiles were identified based on different ST and SCCmec types. Kim et al. reported resistant profiles based on MLST [32]. The two major clones ST5-II and ST239-III had differing antibiotic patterns. Of ST5-II isolates, 99% were resistant to erythromycin, 88% to clindamycin, 99% to ciprofloxacin, 93% to gentamicin, 13% to rifampicin, and 4% to trimethoprim-sulfamethoxazole. For ST239-III, all isolates were resistant to erythromycin, gentamicin but 89% were resistant to clindamycin, 98% to ciprofloxacin, 4% to rifampicin, and 88% to trimethoprim-sulfamethoxazole. The CA-MRSA clone ST72 was more susceptible to antibiotics compared to ST5 and ST239 in this study, specifically clindamycin, ciprofloxacin and gentamicin.

Sung et al. reported from tertiary hospitals among CA-MRSA isolates, resistance rates to gentamicin, ciprofloxacin, tetracycline, and trimethoprim-sulfamethoxazole were lower than those of HA-MRSA isolates [71]. Rifampicin and erythromycin resistance rates were similar between CA-MRSA and HA-MRSA, and none of the SCCmec type II or III isolates were susceptible to erythromycin. There were more HA-MRSA clones that were resistant to multiple antibiotics compared to CA-MRSA clones. The vancomycin susceptibility breakpoint used an MIC of $<2\mu g/mL$ in this study, and 6 isolates had an MIC of $\geq 2\mu g/mL$ with 5 of them SCCmec type II and III.
Studies in Japan demonstrated a wide variety of resistance patterns in MRSA isolates from hospital settings across the country. Molecular differences by SCCmec type were seen in the study by Inomata et al. using a POT analysis to predict SCCmec types found similar resistance profiles in isolates by the same SCCmec type [26]. Higher rates of resistance were found in isolates with SCCmec types I, II and III compared to SCCmec types IV and V. The antibiotic resistance rates were similar across all CA-MRSA and HA-MRSA and predicted SCCmec types for penicillin, oxacillin, ampicillin, cefoxitin ceftriaxone, amikacin, rifampicin, trimethoprim-sulfamethoxazole, and arbekacin but differed for the remaining antibiotics tested. All of the 219 isolates were resistant to penicillin, ampicillin, and cefoxitin, but were not resistant to linezolid, teicoplanin, or vancomycin. More than 90% of the isolates were resistant to oxacillin, ceftriaxone, and erythromycin while susceptible to rifampicin, trimethoprim-sulfamethoxazole, and arbekacin. Variability within SCCmec types by PFGE pulsotypes was identified in the study by Nakaminami et al. where multiple pulsotypes of ST764-II, a ST5 variant, had differences in resistance between PFGE pulsotypes [49]. The ST764-II strain found across multiple PFGE pulsotypes was resistant to multiple antibiotics with the epidemic pulsotype I being resistant to fluoroquinolones, macrolides, gentamicin, and minocycline tested in the study.

The Otsuka et al. [54] and Mine et al. [48] studies were conducted on islands which were geographically separate from the mainland of Japan. Otsuka et al. reported 68.3% of MRSA isolates were resistant to gentamicin and erythromycin,
58.5% were resistant to clindamycin, 31.7% to minocycline and 34.1% to fosfomycin. No resistance was observed for arbekacin, trimethoprim-sulfamethoxazole, teicoplanin or vancomycin in all isolates. Mine et al. only conducted antibiotic susceptibility testing on only isolates containing PVL genes, which were typically CA-MRSA [48]. A ST8-IV clone with PVL genes (USA300) was found to have resistance to erythromycin, gentamicin, and levofloxacin indicating the potential difficulty that physicians may find when treating and managing community onset skin and soft tissue infections due to MRSA isolates with PVL genes.
Table 6. Overall antibiotic resistance rates for studies in Japan and South Korea

The table lists all the antibiotics tested for resistance and provides the overall resistance rate (%) for each study in South Korea* and Japan. The percentages represent the resistance rate in all samples from each study which contain combinations of CA-MRSA and HA-MRSA isolates.

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PUBLIC HEALTH PERSPECTIVE

The major countries of East Asia are only a subset of many other countries in a region known to have high levels of antimicrobial resistance [27]. In particular, the burden of MRSA in Asia has been increasing with concurrent increased genetic variation in this bacterium [7,25]. The major Far East countries examined by this literature demonstrate how this region of Asia contains a wide variety of MRSA clones. Across China and Taiwan there is a continued predominance of HA-MRSA clones in hospital settings. The primary concern about these HA-MRSA clones is the potential of these bacteria to obtain genetic components that confer resistance to additional antibiotics at a greater scale. The evidence of genetically novel strains across hospitals in Japan, South Korea, and primarily China, and single locus variants of major clones with greater resistance profiles also validate the issue of greater levels of antibiotic resistance in S. aureus, which has implications in protecting health across populations.

Alongside the evolution of S. aureus obtaining antibiotic resistance phenotypes, the invasion of genetically unique strains from the community into hospitals is currently occurring in Asia. The presence of MRSA in Chinese and Taiwanese healthcare centers is characterized by ST239-III and ST5-II strains which have been historically predominant. However increased reports of CA-MRSA clones in hospitals is noted by the emergence of ST59-IV/V clones in these settings. Typical HA-MRSA clones in Japan and South Korea such as ST5-II are becoming overshadowed by local and foreign CA-MRSA clones such as ST59-IV,
ST72-IV and ST8-IV. The specific concern for CA-MRSA in hospital settings is the acquisition of multi-drug resistance characteristics typically seen in HA-MRSA strains. The possibility of a widely pervasive international CA-MRSA clone obtaining high levels of antibiotic resistance fits the pandemic profile that can threaten public health at a global level. This literature review demonstrates the high level heterogeneity of antibiotic resistance across hospitals in the major Far East countries. With the continual development of technology to accurately characterize genetic and molecular features of MRSA, timely techniques with clinical relevance will be important for making informed treatment choices to not only ensure the recovery of the patient but also to provide accurate surveillance that can track the evolution of MRSA temporally and over geographic areas. These new developments in technologies can help improve tracing and infection control in outbreaks occurring outside of healthcare settings. The ability of molecular characterization techniques to identify and differentiate clones will be a fundamental tool in understanding risk factors associated with MRSA infection unique to the major Far East countries. Individual countries should develop and strengthen surveillance programs within hospitals and communities.

As the region of Asia is comprised of a wide variety of different countries, cultures, peoples, and health systems it is difficult to construct a uniform strategy to combat MRSA and other pathogens with high antibiotic resistance potential. In order to control the continued emergence of MRSA in this continent, a focused effort towards collaborative surveillance across Asia must be a priority in order to
decrease the overall burden of MRSA in the region and slow the progression of antibiotic resistance. Data on MRSA in countries outside of China, Japan, Hong Kong, Taiwan, and South Korea is lacking and further collaborative research should be conducted for high risk populations to understand the full extent of the health burden caused by MRSA across Asia.

Especially in the age of globalization and high volumes of international travel, it is not surprising there is evidence for the clonal dissemination of MRSA within and between countries of different continents. Abundant evidence demonstrating the role of globalization was found through in multiple studies through this literature review. For example, the isolates found in a Shenyang hospital from the northeastern region of China are similar to HA-MRSA strains in the adjacent country of South Korea [75]. Moreover, the study reporting the dominant United States CA-MRSA clone ST8-IV strain with PVL genes (USA300) in South Korean hospitals [37] and, in Japan, the potential source of ST8-IV strains on the island of Okinawa is a local United States military base [48]. In addition, half of the staff in the nursing homes studied by Tsao et al. in Taiwan were long-term foreign workers and the results suggested that these workers are a potential risk factor for MRSA carriage; brings the question whether foreign long term care workers should be screened for MRSA carriage in these environments [76].

Prevention and control are important considerations to decrease the incidence and burden disease caused by MRSA. Resources allocated to screening for MRSA should be directed by information based on the combination of known
epidemiological risk factors and molecular evidence. Environments of close contact, poor hygiene or sharing of equipment should have more rigorous prevention programs. For outbreaks, screening should be mandatory especially in hospital settings and an emphasis on extensive environmental and fomite surveillance should also be considered.

An important consideration which was not covered in this literature review is the role of livestock in MRSA carriage and transmission to humans. MRSA has been known to infect a wide range of animal species including common agricultural livestock [82]. There are previous reports of human infection from livestock-associated MRSA strains and there is a recent influx of literature on this topic [11, 82]. As Asia supports a large proportion of the world's total livestock, the potential for more zoonotic infections is possible. Livestock-associated MRSA may add another layer to the blurring between community- and hospital-associated MRSA infections.
CONCLUSION

MRSA has established itself as a successful pathogen that has and continues to emerge in countries throughout the world. The decreasing reliability of an epidemiological definition of MRSA and evidence for the invasion of CA-MRSA clones into hospital settings in East Asia emphasizes the importance of molecular characterization to accurately identify MRSA isolates for clinical and public health decisions. There is a wide genetic variety of MRSA clones in the Far East and high levels of antibiotic resistance. Existing surveillance systems should be strengthened to detect molecular changes of major MRSA clones and to identify novel strains circulating in the hospital and in communities. Countries lacking information on local MRSA infections should allocate resources to investigate predominant MRSA clones within their borders to contribute to the growing body of knowledge of MRSA in Asia. Finally coordinated efforts between countries should be pursued to conduct appropriate surveillance to understand the etiologies and movement of successful MRSA clones in this region.
BIBLIOGRAPHY


EDUCATION

Sept. 2014 – Present
Boston University (Boston, MA, USA)
Master of Science / Master of Public Health (M.S. / M.P.H.) Candidate
Medical Sciences / Environmental Health
• MPH Functional Certificate: Environmental Hazard Assessment
• MPH Context Certificate: Infectious Disease

Sept. 2008 – May 2013
Western University (London, ON, Canada)
Bachelor of Medical Sciences (BMSc)
Honors Specialization in Medical Biophysics
• Undergraduate Thesis: “Gene-based contrast for MRI: influence of MagA expression on transferrin receptor and iron uptake”

SUMMARY OF SKILLS

• Proficient in computer software in both Windows and Mac OS: Microsoft Office Suite (Word, Excel, PowerPoint), ArcGIS, MATLAB, Photoshop, R, SAS
• Experienced in scientific literature citations and writing (PubMed, MEDLINE), data & statistical analysis, spatial analysis, exposure assessment, digital image processing and basic computational modeling

WORK & RESEARCH EXPERIENCE

Sept. 2016 – Present
Boston University School of Public Health (Boston, MA, USA)
Graduate Teaching Assistant
• TA for Public Health Core PH 717: Quantitative Methods for Public Health
• Primarily responsible for facilitating R lab sessions, responding to students’ questions and grading

May 2016 – August 2016
Boston University School of Public Health (Boston, MA, USA)
Graduate Research Student
• BUSPH Summer Practicum: “Skin and Soft Tissue Infections in US Emergency Departments Visits: a focus on the Homeless”
• Conducted a literature review on high-risk populations for Methicillin-resistant S. aureus (MRSA) infection, executed data analysis in R using national datasets and produced a manuscript report on findings
Sept. 2012 – April 2013
Lawson Health Research Institute (London, ON, Canada)
Undergraduate Research Student
• Provided technical support in developing Western blot and immunohistochemistry methodology on MagA expression and cellular iron metabolism for the application of MRI gene-based contrast (http://dx.doi.org/10.3389/fmicb.2014.00029)

Western University (London, ON, Canada)
Research Project
• Created computational models in MATLAB to determine the effect of capillary geometry on tissue hemoglobin levels for optical imaging methods

Pegasus Capital Management (Oakville, ON, Canada)
Junior Financial Analyst
• Research and monitoring of pharmaceutical and biotech sectors
• Produced weekly forecast summaries with spreadsheet analysis

COMMUNITY AND VOLUNTEERING
Sept. – Dec. 2015
Massachusetts General Hospital: Radiation Oncology Hospitality (Boston, MA USA)
• Weekly volunteering in the Radiation Oncology Department
• Welcomed and conversed with patients and family members during wait times
• Managed hospital gowns and refreshments for patients

Jun. 2014
Projects Abroad: Medical Clinic Volunteer in Peru (Cusco, Peru)
• Assisted physicians in the ICU and on-call emergencies throughout the city
• Primarily was responsible for checking vital signs and acting as a language mediator between clinic staff and foreign patients

Nicaragua Outreach Trips (Managua, Nicaragua)
• Supervised and was responsible for decisions regarding team logistics, health and safety while in Nicaragua
• Worked in impoverished rural and urban settings with church teams to positively impact the local communities.
• Provided food, clean water and services to the homeless, visitations to the oncology ward in a children’s hospital and educational lesson plans for elementary school student