A Mathematical Model For Optimal Admission Screening For Methicillin Resistant Staphylococcus aureus In Acute Care Facilities

Simmonds, Kimberley Anne

http://hdl.handle.net/11023/2777
doctoral thesis

University of Calgary graduate students retain copyright ownership and moral rights for their thesis. You may use this material in any way that is permitted by the Copyright Act or through licensing that has been assigned to the document. For uses that are not allowable under copyright legislation or licensing, you are required to seek permission.

Downloaded from PRISM: https://prism.ucalgary.ca
A Mathematical Model For Optimal Admission Screening For Methicillin Resistant

*Staphylococcus aureus* In Acute Care Facilities

by

Kimberley Anne Simmonds

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE
DEGREE OF DOCTOR OF PHILOSOPHY
GRADUATE PROGRAM IN COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

JANUARY, 2016

© Kimberley Anne Simmonds 2016
Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common healthcare associated infections (HAIs) worldwide. It has both an economic and personal cost to the healthcare system and infected individuals. Admission screening for MRSA is one method to detect MRSA entering the acute care system. Screening combined with isolation is currently a common method for preventing MRSA transmission in Alberta acute care facilities. There remains uncertainty about the best methods to screening patients for MRSA. Universal screening is the testing of all patients admitted to the hospital, regardless of their risk of MRSA colonization; conversely targeted screening only tests a selected patient population considered at greatest risk for MRSA colonization.

Mathematical models for infectious diseases, such as MRSA, are very useful for predicting outcomes with varying scenarios. The purpose of this project was to develop and validate a deterministic differential equations model for MRSA transmission to determine the optimal screening method for the detection of MRSA infected individuals entering acute care facilities. Based on the local epidemiology used to develop this model, the conclusions drawn from the model are that targeted screening of 70-90% of high-risk patients will reduce unidentified-infected MRSA positive individuals. However, this Alberta model that shows a targeted screening program for high-risk individuals with horizontal measures to reduce the hospital transmission rate is the most effective way to reduce MRSA in Alberta acute care facilities.
Acknowledgements

Firstly, I would like to thank Dr. Elizabeth Henderson for her continuous support of my academic studies. Her patience guided me through the research and writing of this thesis. I could not have imagined having a better advisor and mentor for my PhD study.

Besides my advisor, I would like to thank the rest of my thesis committee: Dr Laupland, Dr Joffe, Dr Svenson, Dr Dean and Dr Li for their insightful comments, encouragement and even for asking the tough questions.

Finally I would like to thank my husband who tolerated this whole crazy process, and Betsy Varughese who helped me to learn Mathematica with patience and kindness.

I am grateful to one and all, who directly or indirectly, allowed me to finally complete my thesis.
List of Tables

Table 2.1 Selected Papers on MRSA Screening Programs .......................................................... 34
Table 2.2 Descriptions of Common Mathematical Terms .......................................................... 38
Table 4.1: Data Sources for the Model .................................................................................... 54
Table 4.2: Model Assumptions ................................................................................................. 56
Table 4.3: High-risk Group Definitions .................................................................................... 58
Table 4.4: MRSA Risk Group and Associated Population Numbers (2010-2011 average) ....... 59
Table 4.5: Acute Care Admissions by Risk Group for 2010-2011 (average) ............................. 59
Table 4.6: Monthly Admissions by Risk Category, 2010-2011 (average) ............................... 60
Table 4.7: Average Incident Cases of MRSA by Case Classification ....................................... 62
Table 4.8: Average Incident Cases of MRSA, For Low and High Transmission ......................... 63
Table 4.9: Model Parameters ..................................................................................................... 68
Table 5.1: Changing the Hospital Transmission Rate ($\beta$) ..................................................... 78
Table 5.2: Changing the Community Transmission Rate ($\varepsilon$) ........................................... 80
Table 5.3: Changing both Transmission Parameters ................................................................. 82
Table 5.4: Changing the Admission Screening: High-risk screening ($\alpha$)............................... 83
Table 5.5: Changing both Admission Screening Levels ............................................................ 84
Table 5.6: High-risk Hospital Setting ........................................................................................ 85
Table 5.7: High-risk Community Setting .................................................................................... 87
List of Figures and Illustrations

Figure 2.1: The Epidemiological Triangle for HA-MRSA................................................................. 15
Figure 2.2: Canadian MRSA strains and Corresponding Names ..................................................... 21
Figure 3.1: S-I-S Model for MRSA ..................................................................................................... 46
Figure 3.2a: Hospital Portion of the Compartmental Model of MRSA Screening.............................. 47
Figure 3.2b: Community Portion of the Compartmental Model of MRSA Screening....................... 48
Figure 3.3: Compartmental Model of MRSA Screening in Alberta..................................................... 51
Figure 5.1: Number of Patients in the Acute Care Facility by Month............................................... 72
Figure 5.2: Number of MRSA Positive Individuals Identified on Admission to an Acute Care Facility by Month.............................................................................................................. 72
Figure 5.3: Distribution of Individuals in an Acute Care Facility by MRSA Status, by Month ........... 73
Figure 5.4: Distribution of Individuals in the Community by MRSA Status, by Month ................. 74
Figure 5.5: Probability Distribution of $\beta$ using MCMC................................................................. 75
Figure 5.6: Probability Distribution of $\varepsilon$ using MCMC............................................................... 75
Figure 5.7: Sensitivity Analysis for $\beta$ using LHS, Total MRSA Identified on Admission .............. 76
Figure 5.8: Sensitivity Analysis for $\varepsilon$ using LHS, total MRSA Identified on Admission ............ 77
Figure 5.9: Modeled Relationship between Hospital Transmission ($\beta$) and Individuals who are Isolated, Infected and Identified on Admission in Acute Care facilities ........................................... 79
Figure 5.10: Modeled Relationship between Community Transmission ($\varepsilon$) and Individuals who are Isolated, Infected and Identified on Admission in Acute Care facilities .............. 81
Figure 5.11: Modeled Relationship between Admission Screening and Individuals who are Isolated, Infected and Identified on Admission in Acute Care facilities .......................... 84
Figure 5.12: MRSA Identified on Admission in High Hospital Transmission Setting .................... 86
Figure 5.13: MRSA Identified on Admission in Low-Hospital Transmission Setting.................... 88
Figure 5.14: HA-MRSA per month with Universal Screening......................................................... 89
Figure 5.15a: HA-MRSA with 10% High-Risk Admission Screening .............................................. 90
Figure 5.15b: HA-MRSA with 30% High-Risk Admission Screening ............................................. 91
Figure 5.15c: HA-MRSA with 50% High-Risk Admission Screening ........................................ 91
Figure 5.15d: HA-MRSA with 60% High-Risk Admission Screening ........................................ 92
Figure 5.15e: HA-MRSA with 70% High-Risk Admission Screening ........................................ 92
Figure 5.15f: HA-MRSA with 90% High-Risk Admission Screening ........................................ 93
Figure 5.16a: HA-MRSA with a 20% Reduction in Hospital Transmission ................................. 94
Figure 5.16b: HA-MRSA with a 10% Reduction in Hospital Transmission ................................. 94
Figure 5.16c: HA-MRSA with a 20% Increase in Hospital Transmission ................................. 95
Figure 5.16d: HA-MRSA with a 30% Increase in Hospital Transmission ................................. 95
List of Symbols and Abbreviations

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Susceptible in hospital</td>
</tr>
<tr>
<td>I</td>
<td>Unidentified-infected in hospital</td>
</tr>
<tr>
<td>A</td>
<td>Isolated in hospital</td>
</tr>
<tr>
<td>S_{HR}</td>
<td>Susceptible high risk</td>
</tr>
<tr>
<td>I_{HR}</td>
<td>Infected high risk</td>
</tr>
<tr>
<td>S_{LR}</td>
<td>Susceptible low risk</td>
</tr>
<tr>
<td>I_{LR}</td>
<td>Infected low risk</td>
</tr>
<tr>
<td>\rho_1</td>
<td>Admission rate for the high risk population</td>
</tr>
<tr>
<td>\rho_2</td>
<td>Admission rate for the low risk population</td>
</tr>
<tr>
<td>\beta</td>
<td>Hospital transmission rate</td>
</tr>
<tr>
<td>\varepsilon</td>
<td>Community transmission rate</td>
</tr>
<tr>
<td>\alpha</td>
<td>Successful screening rate in high risk (HR) population</td>
</tr>
<tr>
<td>\delta</td>
<td>Successful screening rate in low risk (LR) population</td>
</tr>
<tr>
<td>d</td>
<td>Discharge rate</td>
</tr>
<tr>
<td>r</td>
<td>The proportion of discharged individuals back to the low risk population from I</td>
</tr>
<tr>
<td>q</td>
<td>The proportion discharged individuals back to the low risk population from S</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>ACCS</td>
<td>Alberta Ambulatory Care Classification System</td>
</tr>
<tr>
<td>ACCIS</td>
<td>Alberta Continuing Care Information System</td>
</tr>
<tr>
<td>AHCIP</td>
<td>Alberta Health Care Insurance Plan</td>
</tr>
<tr>
<td>AHS</td>
<td>Alberta Health Services</td>
</tr>
<tr>
<td>APIC</td>
<td>Association for Professionals in Infection Control and Epidemiology</td>
</tr>
<tr>
<td>ARO</td>
<td>Antibiotic Resistant Organism</td>
</tr>
<tr>
<td>CA-MRSA</td>
<td>Community-Acquired Methicillin-Resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>CARSS</td>
<td>Canadian Antimicrobial Resistance Surveillance System</td>
</tr>
<tr>
<td>CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CNISP</td>
<td>Canadian Nosocomial Infection Surveillance Program</td>
</tr>
<tr>
<td>DAD</td>
<td>Alberta Discharge Abstract Database</td>
</tr>
<tr>
<td>DIAL</td>
<td>Data Integration for Alberta Laboratories</td>
</tr>
<tr>
<td>EARSS</td>
<td>European Antimicrobial Resistance Surveillance Network</td>
</tr>
<tr>
<td>HAI</td>
<td>Healthcare Associated Infections</td>
</tr>
<tr>
<td>HCA-MRSA</td>
<td>Healthcare Associated Methicillin-Resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>HA-MRSA</td>
<td>Hospital-Acquired Methicillin-Resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Units</td>
</tr>
<tr>
<td>IPC</td>
<td>Infection Prevention and Control</td>
</tr>
<tr>
<td>LHS</td>
<td>Latin Hypercube Sampling</td>
</tr>
<tr>
<td>MCMC</td>
<td>Markov Chain Monte Carlo</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin-Resistant <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>NHSN</td>
<td>National Healthcare Safety Network</td>
</tr>
<tr>
<td>ODE</td>
<td>Ordinary Differential Equation</td>
</tr>
<tr>
<td>SHEA</td>
<td>Society of Healthcare Epidemiology of America</td>
</tr>
</tbody>
</table>
CHAPTER 1
INTRODUCTION
THE PROBLEM AND ITS IMPORTANCE

Infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) are one of the most common healthcare associated infections (HAIs) worldwide and are responsible for significant morbidity and mortality. Admission screening for MRSA colonization is one method of identifying cases of MRSA so patients can be isolated and transmission prevented. Cases of MRSA acquired in the hospital are termed hospital-acquired methicillin-resistant *Staphylococcus aureus* (HA-MRSA). Currently, there is no screening standard for acute care facilities at the provincial, national or international levels.

The increasing prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) and its spread through the healthcare system elevates the importance of screening for MRSA on admission to acute care facilities. The changing epidemiology of CA-MRSA makes it ideally suited for mathematical modeling. A mathematical model is very useful for predicting outcomes with varying scenarios, such as various types of screening programs. A model allows for the best screening method based on the local epidemiology of MRSA in Alberta. This model can assist in the determination of the optimal screening method to identify MRSA entering the hospital setting.
RESEARCH PROBLEM & OBJECTIVES

The purpose of this project is to develop and validate a deterministic differential equations model for MRSA transmission to determine the optimal screening method for the detection of MRSA infected individuals entering acute care facilities.

Specific Objectives:

1. To develop a deterministic differential equations model that describes the transmission dynamics of MRSA entering acute care facilities in Alberta.

2. To validate the model via simulations using data from selected acute care facilities in Alberta.

3. To establish criteria for an optimal admission screening method that is most efficient based on the model predictions.

4. To assess and predict which admission screening method is most efficient in Alberta acute care facilities, with varying CA-MRSA and HA-MRSA transmissions rates.
CHAPTER 2

REVIEW OF THE LITERATURE

Methicillin Resistant *Staphylococcus aureus* Infections

Healthcare-associated infections (HAI) are adverse events resulting from interactions with the healthcare system\(^1\). Infection resulting from methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common HAIs worldwide and is responsible for significant morbidity and mortality\(^2,3\). The negative impact of MRSA infections on patients and the cost to the healthcare system underscore the importance of controlling MRSA in acute care facilities. The direct of MRSA infected patients is 1.5-3 times greater compared to their non-infected counterparts\(^4\). In Canada, the most recent estimates are that the direct health care cost attributable to MRSA was $82 million in 2004\(^5\).

MRSA refers to *Staphylococcus aureus* bacteria that are resistant to methicillin/oxacillin antibiotics. This resistance, and resistance to other beta-lactam antibiotics, is encoded by the *mecA* gene, which is situated on a mobile genetic element, called the Staphylococcal Cassette Chromosome mec (SCCmeC)\(^6\). To date, eleven types of SCCmeC (I-XI) have been identified, and several variants of these SCCmeC types have been described\(^7\). Types I-III are considered traditional hospital acquired strains while the smaller MEC types IV-V are considered to be community acquired\(^8\).

Simply put, hospital acquired MRSA (HA-MRSA) is MRSA that is transmitted to a patient while they are in a hospital. In practice, there are differences in the application of this definition between countries, provinces or states within countries, and facilities. Many Canadian acute care facilities use the Canadian Nosocomial Infection Surveillance Program (CNISP) definition of HA-MRSA. It is based on the infection control professional’s assessment of the
following: length of time in hospital prior to MRSA identification (greater than 48 hours), previous MRSA status, prior hospitalization history (previously admitted in past 12 months) and from where the patient has been admitted. Acute care facilities in Alberta align their surveillance criteria to the CNISP criteria, with only minor deviations. In Alberta there are MRSA cases defined as truly hospital acquired and those that are associated with healthcare but the exact location of MRSA acquisition is unclear. These are termed healthcare associated (HCA) and refer to a case that is: 1) not definitively HA, 2) was previously admitted to any acute care facility in the past 12 months, or 3) has a medical device, or 4) was a resident at a continuing care facility in the past 12 months, or 5) was known to have surgery or dialysis in the past 12 months.

In the United States, the Centers for Disease Control and Prevention (CDC)’s National Healthcare Safety Network (NHSN) recent definition for MRSA and other multi-drug resistant organisms have changed slightly from previous years. The NHSN now uses the term Healthcare Facility Onset (HO) to refer to specimens collected more than three days after admission. Previously HO would have been referred to as HA-MRSA. These slight variations in defining hospital acquired or healthcare associated exist worldwide.

**Epidemiology of Hospital Acquired MRSA**

Traditionally, MRSA acquisition results from hospitalization and interaction within the healthcare setting. Antibiotic pressure, which selects for resistant *Staphylococcus*, the intensity of patient care and a pool of susceptible hosts makes the hospital setting the most common place to acquire MRSA. This classic epidemiological triangle (Figure 2.1), with the host-agent-environment interaction, helps to illustrate how infectious diseases such as MRSA are spread and how factors can impact this spread. It requires a susceptible host and an infective agent, in an
environment that brings them together: MRSA as the agent, humans as the host, and the hospital as the environment.

Figure 2.1: The Epidemiological Triangle for HA-MRSA

In terms of the epidemiological triangle, each of the host (patient) specific risk factors increases the susceptibility of the host to MRSA infection. Despite the decades of data collected on this common HAI there remains some debate on the full spectrum of risks and the relative importance of each risk factor and what combination of risk factors are important or are required for acquiring MRSA in the hospital\textsuperscript{11}.

Some of the primary risk factors for HA-MRSA include: previous admission to hospital, being a resident in a long term care facility, comorbidities, colonization pressure, advanced age, length of stay prior to colonization, ratio of healthcare workers and bed occupancy levels, having invasive procedures and indwelling medical devices\textsuperscript{12,13,14,15,16}. Some of these factors, for instance, age and comorbidities (congestive heart failure, diabetes, pulmonary disease, immunosuppression, and renal failure) are patient driven factors that affect the probability that an individual will become colonized or infected with MRSA. Other system type risk factors such as
colonization pressure (number of MRSA-carrier patient-days divided by the total number of patient-days), length of stay prior to colonization and the ratio of nurses to patients and bed occupancy levels have varying levels of association with acquiring MRSA in hospital\textsuperscript{17,18,19,20,21}. These system factors increase the probability of a patient being exposed to MRSA either via environmental exposure or healthcare worker hands.

The weight of the evidence to support the HA-MRSA risk factors varies and is dependent on the local epidemiology, which includes the characteristics of the population and the design of the healthcare system. The age of the population, health of the population, nature of the healthcare system, public or private, and size of facilities can influence MRSA transmission dynamics. This variability in risk factors is also seen in the variability of MRSA rates in the world\textsuperscript{22}. In many hospitals worldwide MRSA is endemic and until recently there was concern that this would remain a permanent situation.

Healthcare associated MRSA has been increasing since the 1970s with the US CDC reporting prevalence of \textit{S. aureus} that is resistant to methicillin has increased from under three per cent to up to almost thirty per cent in the early 1990s\textsuperscript{23}. Rates in intensive care units (ICUs), in particular, have increased and remained high with some ICUs reporting prevalence up to 64.4\%\textsuperscript{24}. The reported prevalence numbers are highly variable depending on the patient population and the type of ICU. In fact, in the United States the prevalence of MRSA varies by geography as well as patient population\textsuperscript{25}. Recently in the United States, fewer invasive MRSA infections were reported in hospitals\textsuperscript{26}. The steady increase in rates of community-acquired MRSA (CA-MRSA) has led to a focused effort to assess the situation and prevent and control this new MRSA, which could in turn improve the adherence to prevention measures that reduce both community and hospital acquired MRSA.
Similarly in Europe, the rates of MRSA in the 1990s were higher than ideal, however not as high as the rates in the United States. Rates of MRSA in hospitals across Europe increased throughout the 2000s to varying degrees. The prevalence of MRSA ranged from less than five per cent in Belgium to over forty per cent in Ireland, with the increase varying by geography. According to the European Antimicrobial Resistance Surveillance Network (EARSS) 2008 data, a significant declining trend of invasive MRSA infections was noted in the following countries: Austria, Poland, Latvia, Romania, Italy, France, Belgium and the United Kingdom. Some of these decreases are thought to be due to non-clinical activities including mandatory reporting by some countries including the United Kingdom. Despite declining European rates of MRSA there remains wide variability in the rates of MRSA across Europe and around the world.

In Canada and Europe, the rates of MRSA are decreasing or at least stabilizing. Recent Canadian hospital point prevalence estimates of MRSA showed a reduced MRSA prevalence from 2010 when it was 4.3% compared to 3.9% in 2012. Surveillance data from the CNISP shows that both CA-MRSA and HA-MRSA have remained stable between 2009 and 2013. In the Western provinces the rate of HA-MRSA was 4.75 per 10,000 patient days in 2009 compared to 3.42 in 2013. The prevalence of MRSA has not increased in the past few years. This is in contrast to previous decades of increasing rates of MRSA in Canadian hospitals.

In Alberta hospitals the rates of MRSA are below the Canadian average. When looking at invasive disease specifically, the rates of MRSA are lower than in the United States and the Canadian average. Historically in Alberta, MRSA identified in facilities is often acquired prior to current admission resulting in a continual importation of MRSA cases in the facility.
Alberta does not have the same endemic MRSA in its hospitals as other facilities do in the United States or elsewhere in the world\textsuperscript{43}.

**Epidemiology of Community Acquired MRSA**

The epidemiology of CA-MRSA is less well understood, as it has evolved within the last few years and continues to evolve. Classic CA-MRSA infections occur in individuals without healthcare-associated risk factors. Although CA-MRSA may cause a range of infections characteristic of all *S. aureus*, these patients typically present with a skin and soft tissue infection, or less commonly as necrotizing pneumonia or infections at other body sites \textsuperscript{44, 45, 46}.

Several patient populations have been identified as being at higher risk for CA-MRSA acquisition than the general population. These include, but are not limited to: First Nations, incarcerated, marginalized urban populations including homeless, drug users, HIV positive individuals, recipients of tattoos, military personnel, athletes, and children\textsuperscript{47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58}. These were the first populations to become infected with CA-MRSA and provided valuable epidemiological information about CA-MRSA. The local epidemiology plays an important role in understanding the populations that have higher rates of CA-MRSA.

The factors that contribute to transmission of MRSA in the community have been referred to as the five C’s: cleanliness, crowding, contact, sharing contaminated items, and compromised skin. Cleanliness is important, as the physical environment can be a source of transmission of MRSA; this is especially true when living conditions are crowded. Also, the sharing of contaminated personal items transmits MRSA and compromised skin increases the likelihood that MRSA can be transmitted to an individual following contact with an MRSA colonized or infected individual\textsuperscript{59}. These five conditions often act simultaneously. Specifically cleanliness, crowding, and contact tend to occur together to increase the transmission of MRSA.
Initially, the manifestation and types of populations defined CA-MRSA\textsuperscript{60,61}. The British Society for Antimicrobial Chemotherapy Working Party on Community-onset MRSA infections advised that patients with ‘spider bites’ (furuncles), recurrent abscesses, recent travel to endemic areas and recent antibiotic use or hospitalization to be suspected of having CA-MRSA\textsuperscript{62}. Then the U.S. CDC Strategies for Clinical Management of MRSA in the Community: Summary of an expert’s meeting Convened by the CDC stated that CA-MRSA isolates based on epidemiologic criteria have common bacteriologic characteristics\textsuperscript{59}. The CA-MRSA strains typically share a type IV or V \textit{SCCmec} cassette and the Panton-Valentine leukocidin (PVL) toxin locus; while other community strains have specific toxin genes based on the geographic origin of the strain\textsuperscript{63}. The CA-MRSA strains are generally more susceptible to various classes of antibiotics than hospital-acquired strains, often expressing resistance only to beta-lactams and erythromycin\textsuperscript{64}. There are increasing reports of CA-MRSA strains acquiring more resistance, however it is their high levels of virulence that continue to dominate the literature\textsuperscript{65,66}.

Virulence of MRSA is based on toxins, adhesion ability, and immune evasion mechanisms\textsuperscript{67}. In CA-MRSA, the PVL toxin is thought to be one of the most significant contributors to its virulence, with other toxins playing a role as well\textsuperscript{68}.

Increasingly, the research literature suggests that people can be colonized with community specific MRSA strains\textsuperscript{69,70}. Colonization with PVL-positive strains, typically community acquired, has been associated with further development of soft-tissue infection\textsuperscript{71}. This colonization maybe linked to antibiotic use or selected antibiotics may reduce the duration of colonization\textsuperscript{72,73}. Specifically clindamycin was found to reduce the rate of recurrent MRSA colonization.
As the epidemiology of CA-MRSA continues to change there is a plethora of discussion about what defines community or hospital acquired MRSA: the epidemiology or the microbiology or both\textsuperscript{7475}. Strains of MRSA that are typically community acquired can be defined by their location of acquisition, genotype or antimicrobial susceptibility depending on the study or surveillance system.

There is a standardized nomenclature for endemic MRSA strains found in Canadian hospitals\textsuperscript{76}. There are ten endemic strains of MRSA in Canada (CMRSA 1-10)\textsuperscript{77}. Recently spa typing, which involves sequencing of the polymorphic X region of the protein A gene (\textit{spa}), has become more common as a technique for classifying MRSA. It is advantageous compared to PFGE, as it is rapid, reproducible, and portable\textsuperscript{78}.

Figure 2.2, modified from Leal \textit{et al}, shows the Canadian pulse field gel electrophoresis (PFGE) nomenclature and spa types for common MRSA types in Alberta\textsuperscript{79}. In Figure 2.2 each of the values in the circle represents a spa type. CMRSA 10 and CMRSA 7 are the predominant CA-MRSA strains in Alberta. These correspond to specific spa types; CMRSA 7 with t1508, t128 and t1787 and CMRSA 10 with t648, t024 and t008.
Some of the first reports of CA-MRSA in Canada were from the western provinces (British Columbia, Alberta, Saskatchewan and Manitoba)\textsuperscript{53,80,81}. The first reports were outbreaks that described similar epidemiology and clinical findings as reports from the United States. The two strains that were responsible for these outbreaks were CMRSA 10 and CMRSA 7. Eventually these clones moved to eastern Canada, and now there are cases reported from across Canada\textsuperscript{82,83}.

The two predominant community strains of CA-MRSA (CMRSA 10 and CMRSA 7) are more likely to be susceptible to: erythromycin, clindamycin, tetracycline, ciprofloxacin, gentamicin, rifampin and trimethoprin-sulfamethoxazole compared to HA-MRSA strains\textsuperscript{84}. The
antimicrobial susceptibilities in Canada vary regionally, and are genotype specific. In Western Canada, some of the MRSA infections in hospitalized patients are genotypically CA-MRSA\textsuperscript{85}. This is in contrast to Ontario and Quebec where most of the MRSA is genotypically HA-MRSA, highlighting the importance of local data to support decision-making\textsuperscript{85}.

In Alberta, CMRSA 10 is the most common strain of MRSA causing infection. It represents 53\% of all clinical specimens, is more susceptible to antibiotics than the predominant HA-MRSA strain (CMRSA 2), and is most common in the Northern parts of the province\textsuperscript{86}. In 2006, a province-wide, population-based outbreak investigation of CA-CMRSA 10 was undertaken that found that despite key risk factors existing for many of the infected individuals, there were also many individuals with no known risk factors, suggesting that MRSA is broadly distributed in the population\textsuperscript{87}. Since that time the rates of CA-MRSA in the community have remained steady, indicating that sustained transmission in the general population is not occurring\textsuperscript{88}.

Worldwide CA-MRSA has become increasingly common since the 1990s and has emerged as a significant source of hospital infection during the past decade\textsuperscript{89,90}. In some situations CA-MRSA strains have become the dominant strain of MRSA in facilities\textsuperscript{91,92}. There is difficulty in determining the transmission of CA-MRSA strains in hospital. This is the result of using epidemiological case classifications that classify cases as hospital or community acquired. The transmission may occur in the hospital (making it HA) but the type of strain is CA, blurring the lines between what is considered hospital or community acquired.

It is unclear whether the patients with CA-MRSA strain infections acquired in the hospital have the typical HA-MRSA risk factors. Some studies have found that patients with nosocomial CA-MRSA have fewer hospitalizations and invasive procedures than nosocomial
HA-MRSA\textsuperscript{93, 94}. Others have found no difference in characteristics of patients that have nosocomial MRSA, whether it is from a community or healthcare acquired strain\textsuperscript{95}. Regardless, it is important to prevent MRSA that enters acute care facilities from spreading to the large pool of vulnerable patients.

**Prevention & Control of Hospital Acquired MRSA**

The mechanism of MRSA transmission is well established. It is transmitted from person to person via contact with an infected individual, hands of transiently colonized individuals (typically healthcare workers) or via contaminated fomites\textsuperscript{96, 97}. MRSA can live on fomites for seven days, although the significance of environmental transmission is far less significant than transmission from person to person\textsuperscript{98}.

In nearly all cases, a period of asymptomatic colonization with MRSA precedes infection. Colonized patients may only be transient carriers of MRSA (where they may transmit the organism to healthcare workers) or they may become infected, with the probability of this occurrence influenced by the epidemiological triangle: organism, host, and environmental factors. Because new acquisition of MRSA by an individual is virtually a prerequisite step in subsequent infection, preventing new MRSA infections in hospitalized patients largely depends on reducing the transmission of MRSA\textsuperscript{99}.

There are four primary approaches to preventing and controlling MRSA. They are: 1) reduce antibiotic use (antibiotic stewardship), 2) stop transmission (isolation an hand hygiene), 3) eliminate reservoirs of MRSA (cleaning and decolonization), 4) and identify carriers (screening)\textsuperscript{100}. Each of the approaches alone may not be sufficient to prevent transmission. A combination of interventions may be required to prevent transmission, especially in high
transmission settings. This bundled approach, with screening as the keystone, has been implemented in many facilities worldwide\textsuperscript{101}.

The first approach, antibiotic stewardship, the appropriate use of antibiotics, is critical in the hospital setting and particularly for MRSA. The selection pressure from antibiotics, and fluoroquinolones specifically, are associated with colonization and infection with MRSA\textsuperscript{102}. Conversely, the proper use of antibiotics reduces MRSA colonization\textsuperscript{103}. Educating staff about appropriate antibiotic use coupled with restriction of antimicrobials that can be prescribed, reduces the incidence of MRSA\textsuperscript{104, 105}. Unfortunately the data suggest that antibiotic use is increasing in Canadian hospitals rather than decreasing\textsuperscript{106, 107}.

The exact nature of the relationship between MRSA and antibiotic utilization is not completely understood. Studies exploring the association between antibiotics and MRSA in the hospital setting have been cross-sectional and ecological\textsuperscript{108, 109}. The recent Canadian Antimicrobial Resistance Surveillance System (CARSS) report indicates that Canada has a higher level of antibiotic use than most European countries. The Netherlands has the lowest antibiotic use as well as low rates of MRSA. Making a clear link between antibiotic use and MRSA rates is difficult as there are additional factors at play, such as the search and destroy policy in the Netherlands. However, the data does suggest that higher antibiotic use is associated with the higher rates of MRSA\textsuperscript{110}. The CARSS findings are consistent with a recent European study that reported populations with no antibiotic use have lower odds of MRSA colonization\textsuperscript{111}.

Isolation and contact precautions prevent the transmission of MRSA in an acute care facility. Isolation places the patient in a single room. Cohorting places patients together that are known to be colonized or infected with MRSA in a shared room or area. The U.S. CDC recommends single patient rooms followed by cohorting of patients and if that is not possible, that
MRSA positive patients can be placed in rooms with patients who are at low-risk for acquisition of MRSA and associated adverse outcomes from infection\textsuperscript{112}. Isolation is almost always paired with contact precautions such as the use of gowns and gloves, and proper hand hygiene, which further aim to reduce the transmission of MRSA between patients.

There is conflicting evidence regarding the efficacy of single patient rooms to prevent MRSA transmission. Some studies have not shown a decrease in MRSA acquisition with the use of isolation measures\textsuperscript{113}. Some have found a decrease in MRSA bacteremia but not a reduction in colonization\textsuperscript{114}. Others have found that screening with isolation has been associated with a significant decrease in MRSA\textsuperscript{115,116}. And while not perfect, isolation in single room settings such as the ICU is still superior to no isolation\textsuperscript{117}. A model by Worby et al., found on average, the combination of screening and isolation decreased MRSA transmission by 64% but with high variability between units\textsuperscript{118}. The greater the transmission rates on the unit, the more effective isolation and decolonization are at decreasing the rates of MRSA.

The act of isolating a patient alone in a room is the source of much debate. Morgan et al., found that healthcare worker compliance with hand hygiene was better for care provided to isolated patients on contact precautions compared to non-isolated patients\textsuperscript{119}. However, there were fewer healthcare workers and visitor interactions for isolated patients on contact precautions compared to non-isolated patients, highlighting the potential unintended consequences negative of isolation on the morale of patients.

Isolation of patients is associated with higher incidence of adverse events, such as drug and medical related errors, as well as greater dissatisfaction with care, and less documented care\textsuperscript{120}. In fact, physicians are almost half as likely to examine patients in contact isolation compared with patients not in contact isolation\textsuperscript{121}. This is logical as there is far more effort involved in checking on a patient in isolation compared to those without precautions. The use of isolation as
part of a screening program must consider the negative effects of isolation as well as the efficacy of the intervention at controlling MRSA.

Hand hygiene is the single most effective intervention to reduce the spread of microorganisms, including MRSA transmission, in hospitals\textsuperscript{122,123,124}. Hand hygiene is considered a simple act but actually requires hospital staff to make a decision to perform hand hygiene and then to perform the act in a correct manner. Behavioural factors are one reason that hand hygiene compliance remains low in many facilities worldwide\textsuperscript{125,126}. In light of the complexity of issues that impact hand hygiene compliance, there is debate about how much effort should be expended to improve hand hygiene compliance\textsuperscript{127,128}.

Hand hygiene is often termed a horizontal measure as it is not disease specific and reduces the transmission of many infectious agents rather than targeting a particular organism. This makes it an appealing intervention. There is a movement away from disease specific interventions, towards measures that reduce the transmission of many organisms. Regardless of targeted measures to control MRSA, hand hygiene is an important mechanism to reduce MRSA and other HAIs.

Decolonization has become increasingly popular and been shown to reduce the rates of MRSA and other organisms that colonize the skin\textsuperscript{129}. Decolonization of MRSA carriers (colonized individuals) eliminates the reservoir of MRSA. The process of decolonization involves nasal antibiotics, such as mupirocin, and antibacterial body wash, such as chlorhexidine, and occasionally oral antibiotics\textsuperscript{130}. The chlorhexidine bath has the benefit of reducing MRSA on the skin and also prevents the growth of other organisms that might lead to invasive infections. If successful, decolonization eliminates the agent in the epidemiological triangle preventing disease and further transmission.
Universal decolonization strategies to reduce MRSA, such as daily chlorhexidine bathing for all patients, are most effective in high MRSA prevalence settings, where the most severely ill patients are located, such as in the ICU\textsuperscript{131,132}. In these particular settings the patients are at risk for a variety of infections and the routine skin decolonization may reduce not only MRSA but also reduce blood stream infections or central line infections that can be caused by organisms that colonize the skin\textsuperscript{133,134}.

In the past 5 years the literature has increasingly reported that targeted decolonization is an effective method to reduce MRSA in hospitals\textsuperscript{118,124,125,135,136,137,138,139}. These epidemiological studies have provided good information to create a model that indicated that even at low rates of efficacy, decolonization works better than isolation to reduce MRSA in the hospital\textsuperscript{140}.

Decolonization is more effective in tandem with other infection control initiatives including screening to identify those colonized with MRSA and standard infection prevention and control (IPC) measures such as hand hygiene, contact precautions and patient isolation\textsuperscript{141}. However, in certain patient populations, such as the ICU, universal decolonization may be preferred. Universal decolonization in the ICU outperformed other targeted IPC measures such as isolation and targeted decolonization\textsuperscript{142}.

Despite the success of decolonization, two issues that limit the success of this practice are the duration of hospitalization and reports of resistance. The length of stay of many patients is insufficient for them to complete the decolonization regimen\textsuperscript{143}. Additionally, there is growing evidence of resistance to mupirocin and chlorhexidine\textsuperscript{144}. This limits the effectiveness of decolonization in some patients. One of the concerns about decolonization and universal decolonization in particular is that it could induce or accelerate resistance. Patients colonized
with MRSA with mupirocin or chlorhexidine resistance are more likely to be persistent MRSA carriers, even after decolonization\textsuperscript{145}. The \textit{qacA/B} gene was found in an outbreak strain of MRSA that showed reduced susceptibility to chlorhexidine\textsuperscript{146}. Yet there is no standardized method and no consensus on the definition of chlorhexidine resistance\textsuperscript{147}. This limits the understanding of the severity of the resistance issue. The potential negative consequence of indiscriminate use of any decolonization therapy must be carefully considered.

A bundled approach, termed “search and destroy”, was introduced in Dutch hospitals to reduce MRSA transmission. This policy was aimed at eliminating, or significantly reducing, MRSA rates in their acute care facilities. In order for the policy to be effective it requires the identification of all patients with MRSA entering the hospital and then eliminating the MRSA. The key components of the search and destroy policy are: targeted admission screening of at-risk patients, pre-emptive isolation of these potential MRSA-colonized patients in single rooms until proven negative and decolonization to remove the MRSA once it is identified\textsuperscript{148}. The Netherlands has shown positive results with this policy\textsuperscript{149}.

Others have also found that a bundled approach that includes improved environmental cleaning as part of a bundle also reduces rates of MRSA infection. The use of ultraviolet (PX-UV) room disinfection combined with hand hygiene and active surveillance decreased the rate of HA-MRSA more than 50\%\textsuperscript{150}. The exact combination of the bundle appears to matter less than the overall multipronged approach to reducing MRSA transmission.

Due to the nature of a bundled approach, the extent to which the individual components contribute is difficult to assess. In 2006, a mathematical model by Bootsma \textit{et al.}, aimed to quantify the effectiveness of different infection control measures that are part of search and destroy policy\textsuperscript{129}. They developed a stochastic model with three hospitals and in each hospital
there were 36 general wards and five ICUs with 100% bed occupancy. Patients were either MRSA carriers (infected) or non-carriers (susceptible). The stimulations using their model determined that isolation of MRSA positive patients identified by clinical culture alone, without screening, was found to be insufficient to control MRSA. Screening of high-risk patients is necessary to identify MRSA carriers and was found to be a critical component of the bundle policy. Finally, they found that while hand hygiene reduces the transmission of MRSA in the hospital, decolonization is important to reduce the number of MRSA positive individuals re-entering the hospital on re-admission.

The United States Healthcare Infection Control Practices Advisory Committee (HICPAC) recommends a combination of control measures for MRSA and other multi-drug resistant organisms (measurement and monitoring, education, prudent antimicrobial use, surveillance, infection control precautions to prevent transmission, environmental measures and decolonization) be implemented, either sequentially or all at the same time, and then the impact be reassessed after an adjustment period\textsuperscript{151}. Bundling appears to be of value not only for MRSA but for other resistant organisms as well.

MRSA Screening

The fourth mechanism to reduce MRSA is to identify carriers. Admission screening for MRSA attempts to identify MRSA carriers. Traditionally, MRSA admission screening has involved the testing of asymptomatic patients who may be unknowingly colonized with MRSA and are admitted to hospital. The screening cultures, usually nares and/or groin, are tested and the patients identified that are colonized or infected with MRSA are isolated. Admission
screening is also referred to in the literature as active surveillance cultures (ASC), particularly by those from Europe, and can refer to both targeted and universal screening programs\textsuperscript{152}.

There are two common types of admission screening that are often employed: universal and targeted. Targeted surveillance is screening of patients deemed to be at higher risk for MRSA colonization or infection. The identification of risk groups is thought to be the most effective use of resources. With fewer people screened, screening costs are reduced by applying targeted surveillance rather than universal surveillance\textsuperscript{153}. Many favour it as a more cost-effective and less work than screening of all patients, including those at very low-risk of MRSA colonization\textsuperscript{154}.

There are three common pitfalls to targeted screening: first, varying anatomical sites of MRSA colonization; second, variability of risk factors for MRSA; and finally, difficulty implementing selective screening. The emergence of CA-MRSA has changed the distribution of MRSA in terms of the populations that are colonized or infected, and the body sites that may be colonized and the manifestation of disease. Recent literature suggests that CA-MRSA preferentially colonized the groin area compared to hospital acquired strains of MRSA\textsuperscript{155}. Those who have MRSA colonization outside of the typical anatomical screening sites are less likely to be identified with screening\textsuperscript{156}. Testing of nasal and additional anatomical sites further complicates MRSA screening and increases costs.

The variability of the risk factors for MRSA often depends on the local epidemiology. Literature definitions of high-risk patients are conflicting; Pan \textit{et al.}, found that age over 70 years was a risk factor, while a review by Forster \textit{et al.}, found that only half of the studies found age to be an independent risk factor\textsuperscript{11,157}. As previously noted, there are some factors that are consistent across populations. However, if CA-MRSA continues to spread in the population then
more and more populations will be added to the risk groups leading to changes in who should be screened. A targeted screening tool that does not reflect the local MRSA situation is likely ineffectual at identifying MRSA colonized individuals.

The role of readmission and positivity rates for screening re-admitted patients is also important to understanding which patients need to be screened. It is estimated that an colonized person has a greater than 40% chance of readmission while still infected with MRSA. This is an important factor when considering who should be screened upon re-admission.

Even with the development of a tool and standard practices, health care workers need to be trained on whom to screen, especially for targeted admission screening to ensure everyone who should be screened is screened. Younger patients are less likely to be screened. In every facility there are likely to be times of day or specific risk groups that are not screened due to workload or errors in risk perception.

In contrast to targeted screening, universal screening is the testing of all patients admitted to the hospital, regardless of their risk of MRSA colonization. There is conflicting evidence about the utility of universal screening for MRSA in the prevention and control of MRSA. A plethora of literature exists on the matter, but these studies use different populations, different testing methods, have variable baseline prevalence of MRSA, variable uses of the term prevalence and different epidemiologic methods. This makes a clear consensus difficult to reach.

Universal screening has the theoretical benefit of identifying all patients colonized with MRSA and if patient isolation occurs prior to receiving screening test results, then universal screening can be highly effective. Unfortunately, this strategy is not possible as it is cost
prohibitive and there are usually insufficient single rooms to permit the isolation of all admissions pending a negative laboratory result.

Rapid testing methods have greatly improved the applicability of universal testing. In the ICU, rapid universal identification of MRSA colonized patients with pre-emptive isolation or cohorting of potential cases did reduce MRSA\textsuperscript{160,161}. Universal screening of targeted patient populations such as surgical patients can be useful to determine who should be decolonized prior to surgery\textsuperscript{162}.

The primary weakness of universal screening is cost. Screening of many low-risk patients may not be an efficient use of healthcare resources. Several studies have found universal screening to not be cost effective\textsuperscript{163,164,165}. Others have found that under certain conditions, high MRSA prevalence settings or in certain patient populations, universal screening is cost effective\textsuperscript{166,167}. While in others, the screening is associated with other measures, making it difficult to determine the cost effectiveness of screening alone.

A final concern with universal screening is the logistics of what to do with patients while awaiting results of the screening. If all admissions require the patient to be isolated until MRSA status is clarified and is negative, there will certainly be insufficient isolation rooms. If patients aren’t isolated then other patients may be at risk.

Table 2.1 summarizes selected papers that investigated active admission screening and their key findings. The table was derived from a review of the recent literature using the following key words: MRSA and universal screening. This resulted in 122 articles and was further reduced to the following 13 articles by excluding editorials, guidelines, studies of very poor methodological quality, non-English articles, non-European or North American studies, pediatric or neonatal study populations and by limiting the publication date to the last 8 years.
Many of the more recent studies assessing screening are more methodologically robust than previous studies, which tended to be poorly designed observational studies\textsuperscript{168}. The clustered randomized control trials and mathematical models provide evidence of the effectiveness of MRSA prevention measures\textsuperscript{169}.
<table>
<thead>
<tr>
<th>Authors &amp; Year of Publication</th>
<th>Setting</th>
<th>Design</th>
<th>Baseline Rate</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robotham et al., 2007</td>
<td>Hospital wide</td>
<td>Math Model</td>
<td>0.05% admission positive</td>
<td>Compared to on admission screening, random screening was more effective control strategy when there is an outbreak. A combination of both random and on admission screening is best in non-outbreak conditions.</td>
</tr>
<tr>
<td>Harbarth et al., 2008</td>
<td>Surgery</td>
<td>Crossover</td>
<td>5.1% prevalence</td>
<td>No reduction in the MRSA rate using universal PCR screening compared to no screening.</td>
</tr>
<tr>
<td>Jeyarantnam et al., 2008</td>
<td>Surgery &amp; Medicine</td>
<td>Cluster randomized-crossover trial</td>
<td>4% incidence</td>
<td>Rapid tests are not superior to regular culture tests, but did have an impact on bed usage.</td>
</tr>
<tr>
<td>Robicsek et al., 2008</td>
<td>Multiple sites, Hospital wide</td>
<td>Cohort</td>
<td>8.9% prevalence</td>
<td>Part of a bundle program, decreased rate of MRSA infection</td>
</tr>
<tr>
<td>Hardy et al., 2010</td>
<td>Surgery</td>
<td>Crossover</td>
<td>5.2% prevalence</td>
<td>Rapid screening reduced time but both culture and rapid testing were universal</td>
</tr>
<tr>
<td>Lee et al., 2010</td>
<td>Hospital wide</td>
<td>Math Model</td>
<td>Varying $R_0$ and prevalence of 1-15%</td>
<td>At varying prevalence levels Universal screening is cost effective</td>
</tr>
<tr>
<td>Murthy et al., 2010</td>
<td>Surgery</td>
<td>Cohort</td>
<td>5.1% prevalence</td>
<td>Cost analysis of universal, risk-based and no screening showed that universal screening is not cost effective but could be in a higher prevalence setting</td>
</tr>
<tr>
<td>Reilly et al., 2010</td>
<td>Emergency, Hospital wide</td>
<td>Cohort</td>
<td>7.5% prevalence</td>
<td>Part of a bundle program, inconclusive results. 88% admission screening, could not achieve 100% admission screening.</td>
</tr>
<tr>
<td>Collins et al., 2011</td>
<td>Multiple sites, Varying services</td>
<td>Phased introduction</td>
<td>4.4% prevalence</td>
<td>Part of a bundle program, the huge number of negative tests and few cases that were missed did not justify the cost.</td>
</tr>
<tr>
<td>Hubben et al., 2011</td>
<td>Hospital wide</td>
<td>Math Model</td>
<td>15% (high) and 5% (medium) prevalence</td>
<td>Screening and isolation are effective compared to no intervention.</td>
</tr>
<tr>
<td>Huskins et al., 2011</td>
<td>ICU</td>
<td>Cluster randomized-crossover trial</td>
<td>Incidence of 30 per 1,000 patient-days</td>
<td>Universal screening and isolation were not superior to no intervention.</td>
</tr>
<tr>
<td>Jain et al., 2011</td>
<td>Multiple sites</td>
<td>Cohort</td>
<td>5.4 to 28.1 prevalence</td>
<td>Found screening &amp; isolation to be effective as part of a bundle, resulting in a 62% reduction of healthcare-associated MRSA.</td>
</tr>
<tr>
<td>Robotham et al., 2011</td>
<td>Hospital wide</td>
<td>Math Model</td>
<td>4.5% admission positive</td>
<td>Screening and isolation reduced the transmission but to a lesser extent than decolonization.</td>
</tr>
<tr>
<td>Huang et al., 2013</td>
<td>ICU</td>
<td>Cluster-randomized trial</td>
<td>Variable (3.7% to 11.1%)</td>
<td>Screening and isolation were less effective than decolonization in reducing rates of MRSA.</td>
</tr>
<tr>
<td>Lee et al., 2013</td>
<td>Hospital wide</td>
<td>Cohort</td>
<td>0.8% prevalence</td>
<td>Universal screening with high hand hygiene compliance and selected decolonization was effective.</td>
</tr>
<tr>
<td>Derde et al., 2014</td>
<td>ICU</td>
<td>Interrupted time series study and cluster randomized trial</td>
<td>Variable (data not shown)</td>
<td>Screening and isolation without another intervention is not effective. Hand hygiene compliance of over 75% was correlated with a decrease in MRSA rates.</td>
</tr>
<tr>
<td>Lee et al., 2015</td>
<td>ICU</td>
<td>Interrupted time-series design</td>
<td>3.58% prevalence</td>
<td>Screening and decolonization are associated with a decrease in MRSA infection and mortality.</td>
</tr>
</tbody>
</table>
Universal screening is effective at identifying MRSA colonized patients but it may not be the most efficient method to do so. In certain settings, with high endemic rates of MRSA and with high-risk patients, universal screening may be warranted. In some cases, legislation has been effected that requires universal screening for political reasons. The Association for Professionals in Infection Control and Epidemiology (APIC) and the Society of Healthcare Epidemiology of America (SHEA) do not support legislation to mandate use of active surveillance cultures to screen for MRSA. The continued controversy concerning universal screening limits the ability of organizations such as SHEA and APIC to make recommendations about the optimal screening methods.

Weekly or daily screening of admitted patients occurs in some high-risk units, such as the ICU, and screening of patients upon transfer to another unit can be used to assess the level of transmission that is occurring in a unit and is typically employed in addition to admission screening and other MRSA prevention measures.

Rapid MRSA Screening

The traditional method of screening patients for MRSA is to use a selective culture with enrichment broth that can take 48-72 hours for results. Newer, selective chromogenic agar media reduces the turnaround time to less than 48 hours. Finally, the single-locus polymerase chain reaction (PCR) assays that target the SCCmec region and part of the open reading frame gene (orfX) can provide detection of MRSA in approximately 2 hours, under ideal circumstances. Often, due to cost, these tests are not run immediately and are batched and as a consequence there is a delay in reporting of results.

The rapid PCR test has been reported as having high sensitivity and specificity, with a recent paper finding that the sensitivity/specificity for most molecular tests is 98.3% and
98.9%\textsuperscript{187}. Two common phenotypic screening tests, the cefoxitin disc diffusion and the Vitek 2 cefoxitin screen have sensitivities and specificities of 95% and 97%, and 95% and 94%, respectively\textsuperscript{188}. This is slightly lower than the rapid PCR tests; however in practice the difference may be negligible.

Some studies report false-positives (lower specificity) due to the single-locus nature of the PCR assay that targets the SCC\textit{meclorf}X junction\textsuperscript{189}. The false positives are the result of select Methicillin sensitive \textit{Staphylococcus aureus} (MSSA) strains that have a portion of the \textit{SCCmec} but have a deletion of the \textit{mecA} gene that encodes methicillin-resistance. There continue to be gaps in the literature in the area of rapid testing to determine its value in MRSA control\textsuperscript{190}.

The specificity of the culture and the speed of the PCR are ideal, but in the absence of this option, using multiple surveillance cultures and tests has also been investigated\textsuperscript{191,192}. The use of multiple cultures to detect MRSA is expensive. A recent study found the additional laboratory cost was $2,088 USD per identified patient\textsuperscript{193}. The identification of additional MRSA carriers must be weighed against the additional laboratory work to determine if the intervention was not cost effective.

Ultimately, the aim of the different screening methods is to identify MRSA cases and to support the reduction of MRSA transmission in hospitals. A meta-analysis of rapid MRSA testing and its effect on hospital acquired MRSA found there is heterogeneity in the evidence\textsuperscript{194}. Despite the inconclusive direction of the evidence regarding rapid testing, one report in the analysis showed that rapid testing was associated with a lower rate of hospital acquired MRSA bloodstream infection (BSI). Ultimately, the available resources and the local epidemiology should determine the type of screening program that is implemented.
Not only does the type of screening, targeted or universal, or the type of test (PCR or culture) matter, the anatomical site where the swab was taken from affects detection of MRSA. All mucosal sites including the nares, throat, rectum and other moist areas such as the axilla and groin can be colonized with MRSA. The greater the amount of nasal MRSA carriage an individual has, the greater the likelihood that other anatomical sites are also colonized with MRSA\textsuperscript{195}. The nares are the most frequently colonized site but multiple site screening can improve identification of MRSA\textsuperscript{196}. There are advocates for swabbing at least two sites as part of admission screening\textsuperscript{197}.

**Mathematical Modeling**

One method that is gaining popularity, in assessing the effectiveness of infection prevention and control programs to reduce antimicrobial resistant organisms, is the use of mathematical models. A mathematical model is a description of a system using mathematical language. They can highlight gaps in knowledge and data, identify important factors in disease transmission dynamics and make predictions about interventions or the spread of infectious diseases in a population\textsuperscript{198}. Mathematical models are often used when: there are ethical considerations that would prevent an epidemiologic study, the scale of the study is too large to be feasible, or the goal of the study is to predict events in the future. These models are far less expensive than epidemiologic studies. Mathematical models utilize disparate data from a variety of sources and integrate them to explain relationships\textsuperscript{199}.

Mathematical models are used in many areas of science such as physics, chemistry, biology and epidemiology\textsuperscript{200}. Mathematical modeling of infectious diseases has classically involved determining the epidemic spread of disease\textsuperscript{201}. The basic reproductive number ($R_0$) is the mean number of secondary cases resulting from a typical single infected case, and is used to
Mathematical modeling involves four basic steps: 1) identify the assumptions of the model, the variables to be included and the parameters of the model; 2) develop a model that best describes the relationships between the variables; 3) collect empirical data and fit it to the preliminary model; 4) revise or review the model to ensure it makes conceptual sense, and reproduces real world experiences. Only then is the model complete\textsuperscript{202}. These steps can be followed for developing a model for the transmission of MRSA and the optimal method for identifying and limiting MRSA in acute care facilities.

There are several key terms used in mathematical modeling. Table 2.2 provides a brief description of selected key mathematical modeling terms.

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission parameter ((\beta))</td>
<td>The likelihood of an infectious host will infect a susceptible one following an adequate contact, based on the law of mass action\textsuperscript{203}.</td>
</tr>
<tr>
<td>Basic Reproduction Number ((R_0))</td>
<td>The mean number of cases which one case would produce in a completely susceptible population\textsuperscript{204}.</td>
</tr>
<tr>
<td>Infectives</td>
<td>The state when hosts are infectious in a compartment model.</td>
</tr>
<tr>
<td>Susceptibles</td>
<td>The state when hosts are susceptible to infection in a compartment model.</td>
</tr>
<tr>
<td>Contact Rate</td>
<td>The frequency with which susceptible individuals become infective after contact with infective individuals. Often assumed to be homogeneous, where contacts between hosts are made uniformly and with equal likelihood\textsuperscript{205}.</td>
</tr>
<tr>
<td>Parameters</td>
<td>Variables that determine events between compartments in the model. Model parameters are estimated from empirical data, literature review, expert opinion or model fitting.</td>
</tr>
<tr>
<td>Sensitivity analysis (Latin hypercube sampling)</td>
<td>Latin hypercube sampling (LHS) is a statistical method for generating a distribution of plausible collections of parameter values from a multidimensional distribution\textsuperscript{206}.</td>
</tr>
<tr>
<td>Incidence</td>
<td>The rate at which new infections occur in a population\textsuperscript{207}. It is the same definition used in epidemiology.</td>
</tr>
<tr>
<td>Prevalence</td>
<td>The proportion of individuals with a disease in a specified period of time\textsuperscript{208}. It is the same definition as is used in epidemiology.</td>
</tr>
</tbody>
</table>
One type of mathematical model, a compartment model places individuals in categories (compartments) of infection\textsuperscript{208}. These are typically some combination of: infected, exposed, susceptible, and recovered. In this type of model the population under investigation is divided into the number of compartments in the model. A simple communicable disease model with susceptible, infected and recovered compartments is termed an S-I-R model. Those in the susceptible compartment have not been infected. Once they mix with an infected individual they can move to the infected compartment depending on the transmission rate for the disease in question. Infected are able to transmit disease and may at some point move to the recovered (or cleared of infection) compartment. At any time ($t$) there will be varying proportions of the population in the compartments based on whether the disease is at an endemic, epidemic or has burned out of the population.

Compartment models can be either deterministic or stochastic. A deterministic compartment model uses differential equations to depict the movement between compartments. Kermack and McKendrick founded the deterministic compartmental epidemic modeling for infectious diseases\textsuperscript{209}. The deterministic models use the principle of mass action to move individuals from the susceptible compartment to the infected compartment. The force of infection, based on the principal of mass action, is the number of contacts that result in infection per susceptible individual per unit of time. The force of infection increases, as there are more individuals in the infected compartment, but is bounded by the number of infected individuals\textsuperscript{210}. A simple deterministic model for transmission assumes that: everyone is identical (i.e. there is an equal likelihood of becoming infected), contact is instantaneous, mixing is instantaneous (and is independent of having mixed in the past), the population is large so that division into compartments is always possible and every infection follows the same course\textsuperscript{211}. 

\textsuperscript{208}Kermack and McKendrick's work was foundational in the development of compartment models for infectious diseases.

\textsuperscript{209}In deterministic models, mass action involves the assumption of instantaneous mixing and contact.

\textsuperscript{210}The force of infection is bounded by the population size to ensure realistic outcomes.

\textsuperscript{211}Every infection follows the same course, implying identical behavioral patterns among individuals.
A stochastic model allows the movement of individuals between compartments where model parameters vary based on a probability distribution, where as a deterministic models use parameters based on the average in a population\textsuperscript{212}. In a stochastic model there are transition probabilities from one compartment to another based on the Markov chain process. This process allows for the random or chance effect.

In a situation with a large population, the deterministic model provides a good approximation to the stochastic counterpart if the initial density of infected individuals is greater than zero\textsuperscript{213}. The question under investigation and the setting for the model determine the best model to use. Both deterministic and stochastic models have advantages. Deterministic models provide powerful qualitative results about threshold behaviour. These models also tend to have simpler mathematical questions than the stochastic ones\textsuperscript{214}. Stochastic compartment models are useful for small populations, where there is a greater likelihood of fluctuations simply by chance alone\textsuperscript{215}. Both types of models can be solved analytically or by simulation.

For both deterministic and stochastic models the movement from the susceptible to infected compartment is dynamic. In contrast, there are other models that use a constant probability of infection. Decision tree models and static Markov models, typically used in health economics, use states and there is a probability of moving from one state to another, with a final state (or terminal node) that is the outcome of the model\textsuperscript{216}.

These models work well when there is no transmission dynamics involved, such as in the case of chronic diseases, by identifying sensitive parameters in the model that are good targets for interventions\textsuperscript{217}. However, when an intervention can impact the number of susceptible or infected individuals, which in turn affects the disease transmission, it is important to use a stochastic or deterministic mathematical model, as appropriate. These dynamic transmission
models capture inherent nonlinear relationships in transmission and the indirect benefits of herd immunity for interventions\textsuperscript{218}.

There are several methods used to fit a model. Traditional fitting methods including: least squares and Markov Chain Monte Carlo (MCMC) analysis provides models that are well fit\textsuperscript{219}. Least squares is used to determine the point estimate for both the community and hospital transmission parameters and MCMC method is used for the confidence interval estimation to improves the understanding of the precision of the point estimate.

One of the issues that can arise in the development of a mathematical model is when there is a parameter that cannot be fitted. This non-identifiability occurs when functionally related parameters can’t be separately estimated\textsuperscript{220}. It is the result of only parts of the model being observed directly and the related parameters not being able to be separated. The estimated parameter compares well to one model outcome but provides false results in other model outcomes. Fitting using multiple methods and the availability of multiple data points diminishes non-identifiability issues.

Mathematical models for infectious diseases, such as MRSA, are very useful for predicting outcomes with varying scenarios. They may be compared with experimental results, when available. This comparison usually requires numerical simulations, and the resulting predictions are compared with observed data\textsuperscript{221}. They work well in situations that involve large populations, where experimental or observational studies are too expensive and time-consuming. Models also work well in situations where there are limited data and statistical analysis would be unreliable. For these reasons, models for predicting the transmission rates and patterns of MRSA and other antibiotic resistant organisms have become increasingly common.
Cooper et al., developed a basic model for the spread of hand-borne nosocomial pathogens such as MRSA. The model has four compartments: colonized healthcare workers, un-colonized healthcare workers, colonized patients, and un-colonized patients. Patients and healthcare workers can move between colonized and un-colonized states. Patients can be admitted or discharged. The model is similar to a malaria model with healthcare workers acting as vectors to transmit MRSA between patients to describe the transmission dynamics. In this model with a very small hospital population or a single unit, a stochastic approach is essential.

Robotham et al., investigated the effect of different screening methods, using the same mathematical model as Cooper et al.,. They found that random screening of patients while in the hospital yielded better prevalence estimates and reduced MRSA transmission compared to admission screening.

Bootsma and Bonten used a mathematical model in 2006 to assess different MRSA control strategies, making minor modifications, to assess the search and destroy policy in the Netherlands. This group has produced the most compelling arguments in favour of high-risk screening rather than universal screening and support targeted screening with subsequent isolation and decolonization.

Lee et al., used a mathematical model to examine the effects of outbreaks in one facility on other facilities in the surrounding area. They found that a single outbreak in one ICU lead to an increase in prevalence of MRSA of almost 3% in other facilities. This is important as the other hospitals and community act as reservoirs for MRSA. This highlights how infection control practices must account for the relationship between hospitals.

A mathematical model developed by D’Agata et al., used a deterministic model to look at the replacement of HA-MRSA strains with CA-MRSA strains. They found that the increasing
reservoir of CA-MRSA-infected individuals in the community would be the most significant factor in the increase in CA-MRSA prevalence in hospitals. These findings have implications for the type of screening that is performed; whether targeted screening can identify all of the community cases of MRSA, or if universal screening will be necessary to identify the cases entering the hospital.

More recent mathematical models for MRSA in the hospital setting are stochastic or agent based. McBryde et al., used a stochastic model to show that the transmission of MRSA was sustained through admission of colonized patients and not via transmission occurring in the ICU. The stochastic model is well suited for an ICU setting due to the small number of patients.

More recently agent-based modeling has been used to model nosocomial transmission. This type of model is appealing for hospital scenarios as the agent can have a set of behaviours and patterns of movement that allows the modeler to replicate the diversity of the actual patient population. A recent agent based model was developed to understand the role of MRSA colonized individuals and community MRSA transmission. As computing power improves, and familiarity with agent-based modeling increases, it will become an increasingly common method to model MRSA and other nosocomial pathogens.

Modeling of MRSA screening is imperative because of the potential influx of CA-MRSA into the hospital setting and the changing epidemiology of this pathogen. Screening is one of the most debated issues for MRSA control and prevention. Local data used to develop a model based on the local epidemiology is necessary to provide evidence for good decision-making.
CHAPTER 3
ETHICS, METHODOLOGY & STUDY DESIGN

This study developed a mathematical model to assess various admission-screening methods, with the ultimate goal to decrease hospital cases of MRSA. Chapter 3, the ethics of the data collection, methodology and study design, provides the overview of the model development. The rationale of how the compartments in the model were selected is provided, as is the description of the parameters that allow individuals to transition from one compartment to another.

The steps in the development and validation of the model are:

1. Identify the various components that contribute to a successful MRSA screening program.
2. Identify and list the assumptions and variables to be included in the model.
3. Determine the type of model that best suits the available data.
4. Fit the empirical data to the model. Published and unpublished surveillance data will be required.
5. Estimate the transmission parameters using least squares fitting and using Markov Chain Monte Carlo (MCMC) to determine the precision of the point estimate.
6. Sensitivity analysis using Latin Hypercube Sampling (LHS) to determine how sensitive the model is to changes in the transmission parameters.

The assessment of the various screening methods for the detection of MRSA colonized and infected individuals entering acute care facilities in Alberta was completed after the model development and validation. The success of the screening program was determined by the reduction in the transmission of MRSA within acute care facilities.
Ethics

This research was conducted according to the Tri-Council Policy Statement of ethical conduct for research involving humans and ethics approval was obtained from the University of Calgary. The policy states that researchers’ access to secondary data requires the informed consent of those who contributed data, or an authorized third party. This research was an infection control and surveillance project. Infection Control is a major quality improvement program in health and all rules explicitly stated in the Health Information Act regarding the appropriate collection, use, and disclosures of health information were abided by for this study. Alberta Health Services Infection Prevention and Control is custodian of the surveillance data and access was granted to the data for the proposed research. For this reason, study participant consent forms were not needed.

Privacy, Confidentiality and Data Management

The following steps were taken to ensure that privacy and confidentiality were maintained:

1. All data was in aggregate form and protected in a secure computer. No identifying individual level data was used for this study.
2. Data from Alberta Health was linked using the unique life time identifiers (ULIs) within the databases. Once the linkage was complete all data were aggregated and the data set destroyed.
3. All results are shown in aggregate form and individuals were not identified.

Model Design

The development of the model requires knowledge of the best type of model to fit the disease and an understanding of the epidemiology of the disease. The type of model that forms
the basis of the modeling is based on the nature of the disease. For MRSA, a variation of an S-I-S (susceptible-infected-susceptible) model was selected. Those that are infected with MRSA are able to transmit MRSA to those patients that are susceptible. For the purpose of this model, infection refers to both colonization and infection. The arrow from the susceptible to the infected compartments depicts this movement, as shown in Figure 3.1. It is the transmission parameter (β). The movement back to a susceptible state is the recovery rate (μ). The structure of a generic S-I-S model is as follows: the population as a whole (N) is divided into the 2 groups, susceptible (S) and infected (I). The model tracks the number of people in each of the compartments at any point in time (t).

![S-I-S Model for MRSA](image)

**Figure 3.1: S-I-S Model for MRSA**

The differential equations are as follows:

Susceptible:

\[
\frac{dS}{dt} = -\beta SI + \mu I
\]

Infected:

\[
\frac{dI}{dt} = \beta SI - \mu I
\]

Based on the epidemiology of MRSA, there are two distinct types of MRSA, community acquired (CA) and hospital acquired (HA) MRSA. In the hospital setting, three compartments based on the S-I-S model with isolation were required (see Figure 3.2a). A basic SIS model
makes the following assumptions: Individuals are born into the susceptible group; susceptible individuals are able to acquire disease, after which they move into the infected class. Infected individuals spread the disease to susceptible individuals, and remain in the infected class before moving back into the susceptible class\textsuperscript{230}. In the hospital setting two conditions did not hold true. First is that those that enter the hospital are either infected or susceptible so this was modified in the model. Second is that the infected individuals move to the susceptible state while in the hospital. The duration of MRSA infection exceeds the length of stay in the hospital and so the model does not include a rate of recovery. In addition, the group of infected individuals that are entering the hospital can be removed from mixing with others. This removal is termed isolation.

Figure 3.2a: Hospital Portion of the Compartmental Model of MRSA Screening

The community portion of the model was initially conceptualized as several compartments, based on the epidemiology of CA-MRSA. There are many specific risk groups
that can be collectively seen as distinct populations that are at higher risk of CA-MRSA. In Alberta this includes but is not limited to: Illicit drug users, First Nations and homeless. In addition there is a second high-risk group in the community that is at higher risk of healthcare associated MRSA (HCA-MRSA). These are individuals with indwelling medical devices, such as catheters or who are on dialysis, and residents of long-term care. There is heterogeneity in the community portion of the model as there were initially two high-risk groups in the community setting.

The goal of the modeling was to assess screening as an intervention and determine the best option for screening. An assessment of admission data for those at risk of CA-MRSA or HCA-MRSA indicated that both of these groups are more likely to be admitted than the general population. As a result, the two high-risk groups in the community were collapsed into a single high-risk group, as shown in Figure 3.2b.

![Diagram of Community Portion of the Compartmental Model of MRSA Screening](image)

Figure 3.2b: Community Portion of the Compartmental Model of MRSA Screening
It was necessary to have a high-risk group in the community, as admission screening is often determined by perceived risk. The inclusion of two risk groups, high and low-risk, in the community increases the complexity of the model. The rationale for the inclusion of heterogeneity is that while simplicity is the goal, the key factors must be included in the model in order to assess the intervention. In the current model individuals are unable to move between low-risk and high-risk groups. Many of the individuals in high-risk groups are unlikely to move into the low-risk group. For example once you are in a long-term care facility you are unlikely to return to the general community setting. It is possible to have individuals increase their risk of MRSA and move to the high-risk group. It was determined that the movement from low to high-risk does not happen in a significant number of cases during the time period of the model.

The transitions between compartments are a combination of probabilities and density dependent force of infection (true rates). The likelihood of admission is strictly based on a constant admission rate and subsequent discharge from the hospital. The admission and discharges are important factors in the model. They allow the movement of individuals between the two settings. If the settings are not connected then there can be no observed effect of one setting on the other.

Visitors, family members of patients, and other groups that move between the community and hospital could also have been added to the model, as they can transmit MRSA. This would have further complicated the model and likely would not have provided additional value, as they are not known to be significant transmitters of MRSA and there is limited data regarding these groups of people.

The transmission rate is a true rate. In the hospital setting there is no heterogeneity (i.e. no risk groups) and all susceptible and infected individuals are equally likely to acquire and
transmit MRSA. Community transmission of MRSA occurs among high-risk individuals. There is no or very minimal transmission among those in the low-risk setting. This is due to the nature of CA-MRSA, which requires those specific factors such as decreased cleanliness with or without crowding that are not as common among the low-risk general population. The model has only two transmission parameters; hospital and community.

There are several factors in the hospital that impact the transmission of MRSA. These factors include: the type of unit in the hospital, ICU or multiple beds in a room unit, or the level of acuity in the hospital, tertiary care or community hospital or even the type of care, surgery or medicine, the patient receives. In this model there is no stratification in the hospital, such as ICU or different types of patients. It is beyond the scope of this work to assess the interventions to reduce MRSA transmission within the hospital. In this model the key factor is the interaction of people potentially having MRSA between the hospital and the community.

The model aims to depict with simplicity the sometimes-complicated epidemiology of MRSA in Alberta as it related to screening on admission to hospital. Those elements that are not relevant to describing admission screening were dropped because they added complexity and were of little value for the assessment of the intervention. A model assessing a different intervention or comparing multiple interventions would look different than the final model developed for this project.

Model Description and Parameters

The model that was developed describes admission screening for MRSA in adult acute care facilities. The admission rate and transmission of MRSA in both the community and acute care facility can be varied to simulate different types of acute care facilities. Various types of admission screening can also be simulated in the model. The focus of the model is on MRSA
admission screening; factors that minimally impact the screening of MRSA are excluded from the model in order to simplify the model.

![Compartmental Model of MRSA Screening in Alberta](image)

**Figure 3.3: Compartmental Model of MRSA Screening in Alberta**

The model has seven compartments as shown in Figure 3.3. There are four in the community setting and three in the acute care setting. The four compartments in the community are: high-risk susceptible individuals (S\textsubscript{HR}), high-risk infected individuals (I\textsubscript{HR}), low-risk susceptible individuals (S\textsubscript{LR}), and low-risk infected individuals (I\textsubscript{LR}). High-risk populations comprised of both the S\textsubscript{HR} and I\textsubscript{HR} are those most likely to become infected with MRSA as they have a higher rate of MRSA transmission within their peer group. For the purpose of this model, infection refers to both colonization and infection.
In the acute care setting there is an equal likelihood of low-risk and high-risk population mixing, and as a result the number of compartments is reduced to three. The three compartments in the acute care setting are: Susceptible (S), Unidentified-Infected (I), and Isolated (A). The unidentified-infected individuals can transmit MRSA to susceptible individuals as they are unidentified as infected and as such they can mix with other patients. Whereas isolated individuals are also infected but do not transmit MRSA to susceptible individuals as they have been removed from mixing with other patients and additional infection prevention and control (IPC) measures are in place to prevent healthcare worker transmission of MRSA.

The size of the acute care facility is fixed and the total number of patients in all compartments within acute care (S, I and A) do not change over time. The proportion of patients in each of the acute care compartments can vary. The acute care facility is assumed to be always at capacity; when patients are discharged the beds are filled by new admissions. The discharges need to be distributed back to the appropriate compartments in the community population. The proportion of individuals from high-risk and low-risk population is a constant proportion of admissions and this is independent of their MRSA status.
CHAPTER 4

DATA ANALYSIS

In this Chapter the data and the subsequent analysis are described. Data sources used for the model development and parameter fitting are listed and are explained. Aggregate data from various sources were combined with evidence from the literature to determine the parameters and the initial conditions of the model. Finally the sensitivity analysis is presented.

Study Population

The entire Alberta population for 2011 was used for analysis. The data was obtained from the Alberta Health Care Insurance Plan (AHCIP) Population Registry Files and includes all registered Alberta residents. The calendar years 2010 and 2011 were used, as these were the most current years with complete data at the time of model development. Two years of data were selected in order to provide more robust estimates.

Data Sources for Model Development

Aggregate data from Alberta Health and Alberta Health Services databases were used for the development and fitting of the model. The seven databases and the data obtained from them are listed in Table 4.1. No individual level or identifiable data was required for the model development.
### Table 4.1: Data Sources for the Model

<table>
<thead>
<tr>
<th>Database Name</th>
<th>Description of the Database</th>
<th>Use in the Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta Health Care Insurance Plan (AHCIP) Population Registry Files</td>
<td>The AHCIP population registry lists all people as of June 30 each year registered with the AHCIP and are eligible to receive publicly funded health services in Alberta. The AHCIP Registry is populated with information collected during the application process for AHCIP coverage. These data are maintained through notification of account holder information changes.</td>
<td>To obtain the total population (N) in the model.</td>
</tr>
<tr>
<td>Alberta Ambulatory Care Classification System (ACCS)</td>
<td>The ACCS is an ambulatory care patient classification system for acute care facilities that collects data on all acute care events in Alberta, including Emergency Department visits.</td>
<td>Used to define homelessness and illicit drug use risk groups for the model.</td>
</tr>
<tr>
<td>Alberta Hospital Discharge Abstract Files (Inpatient files)</td>
<td>The Alberta Discharge Abstract Database (DAD) collects data on all inpatient events in Alberta. This database contains mandatory fields, including up to 25 diagnostic codes, that are extracted and coded according to coding standards set by the Canadian Institute for Health Information (CIHI).</td>
<td>Used to define total admissions for the model.</td>
</tr>
<tr>
<td>Long term care database (Alberta Continuing Care Information System)</td>
<td>The Alberta Continuing Care Information System (ACCIS) is a provincial system collects data of recipients of continuing care from all community and facility-based continuing care programs in Alberta.</td>
<td>Used to define residents of a long-term care facility for the model.</td>
</tr>
<tr>
<td>Alberta First Nations Registry</td>
<td>The First Nations Status Registry is a listing of all AHCIP registrants who have ever been associated with a First Nations Band since 1983. The data are derived from the AHCIP Central Stakeholder Registry. The information was captured as part of the administration of health premiums. Premiums were discontinued in 2009 and the registry maintained prior First Nations status and flags newborns as being First Nation if the mother had previously been identified.</td>
<td>Used to define First Nations Status for the model.</td>
</tr>
<tr>
<td>ProvSurv</td>
<td>ProvSurv is a system used by the Alberta Health Services (AHS) Infection Prevention and Control (IPC) program for surveillance and data management. It contains data on Antimicrobial Resistant Organisms (ARO) in Alberta.</td>
<td>Used to estimate hospital acquired MRSA in specific facilities and in Alberta overall.</td>
</tr>
<tr>
<td>Data Integration for Alberta Laboratories (DIAL)</td>
<td>DIAL is a system used by the Provincial Laboratory for Public Health in Alberta. It extracts and interprets testing data from the Laboratory Information System. It contains first clinical isolate data on MRSA in Alberta.</td>
<td>Used to estimate community acquired MRSA in Alberta.</td>
</tr>
</tbody>
</table>

### Statistical & Mathematical Tools

Data extraction and management were performed using SAS version 9.3. Data were extracted for the following data sets: Alberta Health Care Insurance Plan (AHCIP) Population.
Registry Files, Data Integration for Alberta Laboratories (DIAL), ProvSurv, Alberta Ambulatory Care Classification System (ACCS), Alberta Hospital Discharge Abstract Files (DAD), Alberta Continuing Care Information System (ACCIS) and the Alberta First Nations Registry.

For the creation of ordinary differential equations (ODE), parameter fitting, sensitivity analysis, modeling of various scenarios and subsequent analysis were performed in Mathematica version10. The sliders used to determine the optimal screening for MRSA were created in Mathematica and exported to Microsoft Power Point 2010.

**Assumptions and Variables in the Model**

Mathematical models have assumptions, similar to statistical models. Table 4.2 lists the twelve key assumptions used in order to simplify the model. The rationale and explanation is provided for each assumption.
Table 4.2: Model Assumptions

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital 100% occupancy</td>
<td>This is the reality in Alberta acute care facilities.</td>
</tr>
<tr>
<td>Two groups exist in the community: high and low risk</td>
<td>MRSA is not evenly distributed in the community.</td>
</tr>
<tr>
<td>There is no transmission of MRSA in the low risk community group</td>
<td>The transmission of MRSA in the low risk population is negligible and was eliminated to simplify the model.</td>
</tr>
<tr>
<td>Admission rate=discharge rate</td>
<td>Discharge rates to be determined from admission rates</td>
</tr>
<tr>
<td>Discharge rate is independent of risk group</td>
<td>Patients are discharged when they are deemed ready by their care team. This decision is independent of their MRSA status.</td>
</tr>
<tr>
<td>Isolation capacity is unlimited</td>
<td>Isolation capacity is not limited, as cohorting of MRSA patients is available. The purpose of the model is to assess the screening not to determine within hospital transmission.</td>
</tr>
<tr>
<td>Isolation is perfect</td>
<td>There is no transmission parameter for isolated and susceptible patients in the hospital. Although transmission occurs from isolated patients, the risk is thought to be significantly lower than non-isolated infected patients.</td>
</tr>
<tr>
<td>Isolation is immediate</td>
<td>Once an MRSA infected individual is admitted and identified the isolation is immediate.</td>
</tr>
<tr>
<td>This is a closed population</td>
<td>This reduces the complexity of the model and is not relevant to the key transmission dynamics of this disease.</td>
</tr>
<tr>
<td>Successful screening rate is variable</td>
<td>It is dependent on the uptake of the screening program by staff.</td>
</tr>
<tr>
<td>MRSA clearance in the community</td>
<td>This was estimated based on surveillance data, and other mathematical models. There is limited literature on untreated carriage in the community. It is estimated to be six months of carriage.</td>
</tr>
<tr>
<td>No distinction between HA/CA strains of MRSA in transmission dynamics</td>
<td>The variability in transmission dynamics between different strains of MRSA is not relevant for this model.</td>
</tr>
<tr>
<td>Infections and colonization are the same</td>
<td>For the purpose of this mode infection and colonization are both referred to as infected.</td>
</tr>
<tr>
<td>Transmission occurs via direct contact with an infected individual</td>
<td>This is the predominant manner of transmission of MRSA is via direct contact. Environmental transmission contributes minimally to the transmission dynamics.</td>
</tr>
<tr>
<td>The admission rate is independent of MRSA status</td>
<td>The reason for hospitalization is not typically due to MRSA but other co-morbidities of the patient.</td>
</tr>
</tbody>
</table>
Determining Parameters

High-risk Populations

The model was developed to assess different levels of admission screening. Targeted screening of selected individuals upon admission to a hospital required defined groups that were at higher risk of presenting to an acute care facility while colonized/infected with MRSA. Table 4.3 shows the risk groups identified in the literature for being at higher risk of MRSA infection and the associated case definition used to identify these groups. Based on literature from Western Canada, the groups at high-risk for Community Acquired MRSA (CA-MRSA), where there is persistent transmission in the population are: First Nations people (FN) and the homeless and illicit drug users (IDU)\textsuperscript{231,232}. Long-term care residents are considered at high-risk for healthcare associated MRSA (HCA- MRSA). As they are not hospital-acquired this group was added to the CA-MRSA risk category. Those with at least one previous admission to an acute care facility in the past year were classified as high-risk for hospital acquired (HA-MRSA). The final model has a single HR risk category based on those who are at highest risk of MRSA, regardless of the location of MRSA acquisition.
### Table 4.3: High-risk Group Definitions

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>High Risk Group</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Nations</td>
<td>First Nations</td>
<td>The First Nations registry includes anyone ever having registered with the Alberta Health Care Insurance Plan (AHCIP) as either status First Nation or Inuit. Non-Status Indians and Metis, which can’t be identified in the AHCIP population registry, are not included.</td>
</tr>
<tr>
<td>Community Acquired (CA)</td>
<td>Homeless</td>
<td>Homeless. Any individual seen in ambulatory care, or admitted to a hospital in Alberta, that at the time of care had no fixed address, which is recorded in the database as a postal code beginning with X in 2010 or 2011.</td>
</tr>
<tr>
<td>Healthcare Associated (HCA)</td>
<td>Illicit Drug Use</td>
<td>Any individual seen in ambulatory care, or admitted to a hospital in Alberta, in the 2010 or 2011 calendar year that had a diagnosis indicating IDU, as defined by the following ICD10 codes (F11, F14, F15, F16, F18, F19, T40, T43.6).</td>
</tr>
<tr>
<td>Hospital Acquired (HA)</td>
<td>Previous Admission in the Past 12 Months</td>
<td>Any individual admitted to a hospital in Alberta, in the 2010 or 2011 calendar year with at least one admission in the previous year.</td>
</tr>
</tbody>
</table>

The numeric results of the application of the case definitions used in Table 4.3 are found in Table 4.4. This table shows the average population size of each group and the percent of the overall Alberta population that the group represents for the 2010 and 2011 calendar years combined. The risk groups are not mutually exclusive so the case definition was applied in order as they appear in Table 4.3. Those with no risk factors were the remaining individuals in the population that also represented most Albertans. Those with a previous admission in the past twelve months represented the largest risk group identified.
Table 4.4: MRSA Risk Group and Associated Population Numbers (2010-2011 average)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Population Estimate</th>
<th>Per cent of the Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Nations</td>
<td>130,887</td>
<td>3.40%</td>
</tr>
<tr>
<td>Homeless</td>
<td>1,107</td>
<td>0.03%</td>
</tr>
<tr>
<td>Illicit Drug Use</td>
<td>16,507</td>
<td>0.40%</td>
</tr>
<tr>
<td>Long-term Care Resident</td>
<td>22,798</td>
<td>0.60%</td>
</tr>
<tr>
<td>Admission in previous 12 months</td>
<td>239,581</td>
<td>6.30%</td>
</tr>
<tr>
<td>None</td>
<td>3,402,927</td>
<td>89.20%</td>
</tr>
<tr>
<td>Total</td>
<td>3,813,807</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.5 shows the hospital admission rates for the five MRSA risk groups. For the percentage of admissions attributable to each group, the numerator was the number of admissions in each risk group and the denominator was the total number of admissions in the province. It is important to note that these are admissions and not individuals. Anyone admitted more than once would be counted multiple times.

Table 4.5: Acute Care Admissions by Risk Group for 2010-2011 (average)

<table>
<thead>
<tr>
<th></th>
<th>Monthly Admissions</th>
<th>per cent of 100 Monthly Admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Admission in the Past 12 Months</td>
<td>10,163.00</td>
<td>32.6%</td>
</tr>
<tr>
<td>Long-term Care Resident</td>
<td>1,374.30</td>
<td>4.4%</td>
</tr>
<tr>
<td>First Nations</td>
<td>1,930.50</td>
<td>6.2%</td>
</tr>
<tr>
<td>IDU</td>
<td>803.7</td>
<td>2.6%</td>
</tr>
<tr>
<td>Homeless</td>
<td>160.9</td>
<td>0.5%</td>
</tr>
<tr>
<td>Total All Admission</td>
<td>31,215.40</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.6 shows the admission rate for each of the high and low-risk groups after they were collapsed into their associated risk category (HA-MRSA, CA-MRSA or all). When the
calculations were done the categories overlap, therefore, the numbers in Table 4.6 cannot be
calculated from Table 4.5. A previous hospital admission in the past twelve months and
residents of a LTC facility were classified as high-risk for HA-MRSA, while those who use illicit
drugs, who are First Nations and who are homeless were classified as high-risk for CA-MRSA.
It is important to note that LTC residents almost all had a hospital admission in the previous
twelve months and contribute minimally to the percent of community acquired monthly
admissions. The remaining acute care admissions were among those at low-risk of MRSA
acquisition.

The results show that although those with a previous admission in the past 12 months are
a small part of the overall Alberta populations (6.3%), those that are admitted to an acute care
facility represent almost 35% of total admissions. The proportion of admissions attributable to
the population at high-risk for CA-MRSA is also higher than the proportion of the overall
population they represent.

Table 4.6: Monthly Admissions by Risk Category, 2010-2011 (average)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Admissions (month)</th>
<th>per cent of 100 admissions per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk-Hospital Acquired</td>
<td>10,727.20</td>
<td>34.4%</td>
</tr>
<tr>
<td>High Risk-Community Acquired</td>
<td>2,665.30</td>
<td>8.5%</td>
</tr>
<tr>
<td>High Risk-All</td>
<td>13,392.50</td>
<td>42.9%</td>
</tr>
<tr>
<td>Low Risk-All</td>
<td>17,823.00</td>
<td>57.1%</td>
</tr>
</tbody>
</table>

Transmission Rates

The transmission of MRSA occurs both in the community (transmission parameter=\(\epsilon\))
among the high-risk population, and in the acute care facility (transmission parameter=\(\beta\)). The
transmission of MRSA among low-risk populations in the community is considered negligible
relative to the overall transmission of MRSA and as such is not included in the model.
In the acute care facility hereafter referred to as the hospital, those individuals that are unidentified-infected (I) and are not isolated can transmit MRSA in the hospital to those that are susceptible (S). In this model, those that are identified as MRSA positive on admission are isolated (A) and do not contribute significantly to the transmission of MRSA in the hospital and cannot be infected by a second MRSA strain.

The two transmission parameters were determined by back calculation and then fitted, as they cannot be solved for explicitly. The number of MRSA positive individuals per month identified in hospital was used for fitting the transmission parameters. The numbers of MRSA positive individuals per month, shown in Table 4.7, were obtained from two sources, firstly the AHS IPC Provincial Surveillance Program, which identified MRSA positive individuals in hospital for the years 2011-2012 and Secondly, reports from the Alberta Provincial Laboratory for Public Health reporting of MRSA first clinical isolates which included both hospital and community, for the same time period. Only community-identified strains were included in the first clinical isolate testing as the hospital surveillance data will also include the first clinical isolates from facilities. The fitting, precision estimation, and sensitivity analysis used for estimating the two-transmission parameters hospital (β) and community (ε) are further described in the parameter fitting section.
In order to test the model functioning for high transmission and low transmission facilities, data were obtained from four facilities. AHS IPC Provincial Surveillance Program data from the facilities were combined by hospital type and are shown in Table 4.8. Those identified on admission to an acute care facility are classified as CA or HCA MRSA.

These data were used to estimate the hospital transmission of MRSA (\( \beta \)) and the community transmission of MRSA (\( \varepsilon \)) in Alberta for high and low-risk facilities. Two hospitals in Alberta, one in each of Edmonton and Calgary, were selected as the high transmission facilities. The rationale for selecting two hospitals was to determine how the model would function in a high-risk setting rather than for a specific hospital. Two hospitals in Alberta in the North Zone of the province were selected for the low transmission facilities. Selection of facilities was based on discussion with the Director of IPC Surveillance at AHS.
Table 4.8: Average Incident Cases of MRSA, For Low and High Transmission

<table>
<thead>
<tr>
<th>Hospital Type</th>
<th>Identified on Admission Average by Month (2010-2011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Transmission Facilities</td>
<td>69, 70, 82, 82, 86, 73, 78, 75, 73, 79, 69, 77</td>
</tr>
<tr>
<td>Low Transmission Facilities</td>
<td>13, 11, 12, 23, 28, 12, 21, 21, 15, 17, 20, 18</td>
</tr>
</tbody>
</table>

Admission and Discharges for Specific Populations

The hospital admission rate is different for high and low-risk populations (shown in Figure 3.3). The admission rate is \( \rho_1 \) and \( \rho_2 \) for the low and high-risk groups respectively. Individuals in the high-risk population are more likely to be admitted to the hospital than their low-risk counterparts. The overall number of admissions per month is a constant proportion of the high and low-risk population, while the proportion of each group that is infected with MRSA varies by the transmission in the community. The acute care discharge rate is independent of the risk group and admission rate. The overall discharge rate is determined by the capacity of the acute care facility, with the proportion of people returning to the low and high-risk community group as appropriate. The proportion of individuals that return to the susceptible low-risk compartment is denoted as \( r \) in the model and the proportion that returns to the susceptible high-risk group is denoted as \( 1-r \). The infected individuals are allocated back to the high and low-risk groups in a similar fashion, with the proportion of infected individuals returning to the low-risk compartment as \( q \) and the proportion returning to the high-risk group is \( 1-q \).

Screening

There are two screening parameters, one for the high-risk population (\( \alpha \)) and one for the low-risk population (\( \delta \)). Admission screening of patients for MRSA typically occurs for either all patients admitted to the hospital or for the high-risk group. In the model, screening rates can be altered to investigate different screening scenarios. The successful screening rate is dependent on the proportion of individuals screened and the sensitivity and specificity of the test.
The Vitek 2 system and the cefoxitin disk-diffusion testing are the most common screening tests used in Alberta. Both of the screening test methods have sensitivities between 95-99% and specificity of 100%. Therefore the successful screening rate is primarily influenced by the proportion of admitted patients that are screened rather than the sensitivity of the laboratory test.

**Initial Conditions & Parameter Fitting**

The parameters that are not calculated with empirical data are fitted using non-linear least square methods. The province as a whole is used to estimate the parameters and the unit of time is months. Outside of the hospital the initial conditions for the compartments (I_{HR}, S_{HR}, I_{LR}, S_{LR}) are calculated primarily based upon population data and the acute care admission data sources, whereas the initial conditions for the inpatient data is primarily derived from the Alberta Health Services IPC data including point prevalence and surveillance data. On March 31, 2011 the number of acute care beds in Alberta was 8,009 and the total population of Alberta in 2011 was estimated to be 3,813,807. All of the initial conditions were rounded in the model. The model parameters are shown in Table 4.9.

**Hospital Parameters**

**Estimating Isolation (A):** The number of admitted patients identified with MRSA in any given month is derived from the AHS IPC Surveillance data and the 2010 point prevalence survey data. The average number of MRSA positive individuals identified in a month was approximately 400.

A=400
Estimating Unidentified-Infected (I): The 2010 point prevalence survey data was used to determine the number of previously unknown MRSA positive individuals in the hospital. Five per cent of all admitted patients were positive and not known to be positive.

\[ I = 8,009 \times 0.05 \]

\[ I = 400 \]

Estimating Susceptible (S): Total number of acute care beds less those on isolation (A) and those estimated as infected (I) from point prevalence studies.

\[ S = 8,009 - 400 - 400 \]

\[ S = 7,200 \]

Successful screening rate in high-risk (HR) population (α): The proportion of high-risk admitted patients screened based on the current state in Alberta.

\[ \alpha = 0.7 \]

Successful screening rate in low-risk (LR) population (δ): The proportion of low-risk admitted patients screened based on the current state in Alberta.

\[ \delta = 0.1 \]
Community Parameters

Estimating Infected High-risk (IHR): The IHR population was estimated using the formula for calculating the prevalence of a disease (P) is equal to the incidence of the disease (I) multiplied by the duration of the disease (D). In this scenario there is also the underestimated factor.

\[ P = I \times D \times \text{underestimation factor} \]

I = 230 (average number of people newly identified each month)
D = 6 (average number of months for infection duration)
Underestimation = 10 fold

\[ I_{HR} = 13,800 \]

Estimating Susceptible High-risk (SHR): The SHR population was derived from subtracting the infected high-risk population from the total high-risk population

Total high-risk pop = 337,686

\[ S_{HR} = 337,686 - 13,800 \]

\[ S_{HR} = 323,886 \]

Estimating Infected Low-risk (ILR): The ILR was estimated using the proportion of MRSA positive people identified in previous research and assessing what proportion of them were considered low-risk.

\[ I_{LR} = 13,800 \times 40\% \]

\[ I_{LR} = 5,520 \]

Estimating Susceptible Low-risk (SLR): The SLR population was derived from subtracting high-risk populations (IHR & SHR) and infected low-risk (ILR) from the total population of Alberta.

\[ S_{LR} = \text{Total Population} - (S_{HR} + I_{HR} + I_{LR}) \]

\[ S_{LR} = 3,813,807 - (337,686 + 13,800 + 5,520) \]

66
S_{LR} = 3, 456,801

**Fitted Parameters**

**Estimating d:** Discharge rate for the hospital was fitted and also based on the values of ρ1 and ρ2 and the empirical data which indicates there were approximately 30,000 admissions per month in Alberta.

Discharge rate (d) = 3.937 (fitted)

**Estimating ρ:** The admissions per month in each of the HR and LR groups are approximately 13,000 for the high-risk group and 19,000 for the low-risk group. The proportion of admissions from IHR and ILR is independent of MRSA infection and is a dependent on the size of the IHR and ILR population.

Admission rate for the low-risk population (ρ1) = 2.900 (fitted)

Admission rate for the low-risk population (ρ2) = 1.403 (fitted)

Hospital Transmission Rate (β) = 0.0003677 (fitted)

Community Transmission Rate (ε) = 0.0000004622 (fitted)

The proportion of discharged individuals back to the low-risk population from I (r) = 0.647 (fitted)

The proportion of discharged individuals back to the low-risk population from S (q) = 0.728 (fitted)
### Table 4.9: Model Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible in Hospital (S)</td>
<td>7,200</td>
</tr>
<tr>
<td>Unidentified Infected in Hospital (I)</td>
<td>400</td>
</tr>
<tr>
<td>Isolated in Hospital (A)</td>
<td>400</td>
</tr>
<tr>
<td>Susceptible High Risk (S_{HR})</td>
<td>323,886</td>
</tr>
<tr>
<td>Infected High Risk (I_{HR})</td>
<td>13,800</td>
</tr>
<tr>
<td>Susceptible Low Risk (S_{LR})</td>
<td>3,456,801</td>
</tr>
<tr>
<td>Infected Low Risk (I_{LR})</td>
<td>5,520</td>
</tr>
<tr>
<td>Admission rate for the low risk population (ρ₁)</td>
<td>2.9</td>
</tr>
<tr>
<td>Admission rate for the low risk population (ρ₂)</td>
<td>1.403</td>
</tr>
<tr>
<td>Hospital Transmission Rate (β)</td>
<td>4.62 x 10^{-7} (95% CI 1.56 x 10^{-7} - 4.91 x 10^{-7})</td>
</tr>
<tr>
<td>Community Transmission Rate (ε)</td>
<td>4.62 x 10^{-7} (95% CI 1.56 x 10^{-7} - 4.91 x 10^{-7})</td>
</tr>
<tr>
<td>Successful screening rate in high risk (HR) population (α)</td>
<td>0.7</td>
</tr>
<tr>
<td>Successful screening rate in low risk (LR) population (δ)</td>
<td>0.1</td>
</tr>
<tr>
<td>Discharge rate (d)</td>
<td>3.937</td>
</tr>
<tr>
<td>The proportion of discharged individuals back to the low risk population from I (r)</td>
<td>0.647</td>
</tr>
<tr>
<td>The proportion discharged individuals back to the low risk population from S (q)</td>
<td>0.728</td>
</tr>
<tr>
<td>Hospital Capacity (H)</td>
<td>8000</td>
</tr>
</tbody>
</table>

**Model Equations**

\[
S'(t) = -\beta S(t)I(t) - S(t)d(1-q) - S(t)dq + p_1H\frac{S_{LR}(t)}{S_{LR}(t) + I_{LR}(t)} + p_2H\frac{S_{HR}(t)}{S_{HR}(t) + I_{HR}(t)}
\]

\[
I'(t) = \beta S(t)I(t) - I(t)d(1-r) - I(t)dr + (1-\delta)p_1H\frac{I_{LR}(t)}{S_{LR}(t) + I_{LR}(t)} + (1-\alpha)p_2H\frac{I_{HR}(t)}{S_{HR}(t) + I_{HR}(t)}
\]

\[
A'(t) = \alpha p_2H\frac{I_{HR}}{S_{HR} + I_{HR}} + \delta p_1H\frac{I_{LR}}{S_{LR} + I_{LR}} - A(t)d
\]

\[
I_{HR}(t) = \epsilon S_{HR}(t)I_{HR}(t) - \frac{1}{6} I_{HR}(t) - (1-\alpha)p_2H\frac{I_{HR}(t)}{S_{HR}(t) + I_{HR}(t)} + A(t)d + I(t)d(1-r) - \alpha p_2H\frac{I_{HR}(t)}{S_{HR}(t) + I_{HR}(t)}
\]

\[
S_{HR}(t) = S(t)d(1-q) - p_2H\frac{S_{HR}(t)}{S_{HR}(t) + I_{HR}(t)} - \epsilon S_{HR}(t)I_{HR}(t) + \frac{1}{6} I_{HR}(t)
\]

\[
I_{LR}(t) = I(t)dr - \delta p_1H\frac{I_{LR}(t)}{S_{LR}(t) + I_{LR}(t)} - (1-\delta)p_1H\frac{I_{LR}(t)}{S_{LR}(t) + I_{LR}(t)} - \epsilon S_{LR}(t)I_{LR}(t) + \frac{1}{6} I_{LR}(t)
\]

\[
S_{LR}(t) = S(t)dq - p_1H\frac{S_{LR}(t)}{S_{LR}(t) + I_{LR}(t)} + \frac{1}{6} I_{LR}(t)
\]
Parameter Fitting and Sensitivity Analysis

Several parameters including both the hospital transmission parameter ($\beta$) and the community transmission parameter ($\varepsilon$) were estimated using non-linear least squares parameter fitting methods. The data used for parameter fitting was obtained from published literature and empirical data from local surveillance and point prevalence data. The admission rates ($\rho_1, \rho_2$) and the discharge rates ($d, r, q$) were also fitted parameters. There were two general steps used to simultaneously fit $\beta$ and $\varepsilon$. The first step was to use Latin Hypercube Sampling (LHS) to generate sample points for $\beta$ and $\varepsilon$. The sample points used for model simulation helped estimate the parameter set that had the lowest mean square error. The estimated parameters were then inputted back into the model and the overall model outputs re-assessed. The 95% confidence interval for the $\beta$ and $\varepsilon$ was determined using Markov Chain Monte Carlo (MCMC).

Sensitivity analysis was conducted for $\beta$ and $\varepsilon$. The LHS method was used to generate sample points used in model simulations to assess which parameters when altered had the biggest impact on the model results. The ordinary differential equation (ODE) solver in Mathematica version 10.0.2 was used for all model analysis.

For the transmission point estimation, the estimates of $\beta$ (hospital transmission) reported in the literature are $0.0005 < \beta < 0.01$, with $\varepsilon$ (community transmission) estimated to be much lower, although not quantified $^{167,238,239}$. The least squares method finds the best-fit line for the data. The transmission parameters $\beta$ and $\varepsilon$ were fit to all MRSA positive individuals identified on admission as well as to the range of permissible values for the number of individuals in each of the compartments in the hospital.

The discharge rate and the proportion of patients discharged to the high and low-risk populations ($d, r$ and $q$) were fitted after the transmission parameters. Then the transmission
parameters were fit again to admission and discharge rates ($\rho_1$, $\rho_2$, & d) with estimated ranges based on empiric data, for 500,000 simulations, then the admission and discharge rates were re-fitted using the fitted values for the proportion of patients discharged to the high and low-risk populations ($r$ and $q$) for 500,000 simulations.

Markov Chain Monte Carlo (MCMC) was used to determine the 95% confidence interval for the estimated parameters. Simulations were run for 500,000 samples for each of the transmission parameters ($\epsilon$ and $\beta$). MCMC simulation generates a random sample of points for each uncertain input variable in the model. It selects each point randomly regardless of the probability distribution for that input variable, so there is no pattern of distribution.

Sensitivity analysis using Latin Hypercube sampling (LHS) was performed on the parameters that are most influential to the model outcome based on a reasonable range found in the literature. LHS evenly distributed sample points across all possible values. Each point is placed into intervals of equal probability, so that predetermined triangular probability density distribution is formed. For the sensitivity analysis, the probability density function outcome is the number of MRSA positive individuals identified on admission in a twelve-month period.
CHAPTER 5

MODEL RESULTS

Chapter 5 presents the results of the new Alberta model, which aims to determine the optimal screening for Alberta acute care facilities. These results show the relationship between the parameters for screening, MRSA transmission and the compartments in the hospital.

Initial Results

The model was fitted to empirical data and was constrained to ensure that the size of the acute care facility remained constant. The initial conditions for the three acute care compartments are: susceptible individuals \( S = 7200 \), unidentified-infected individuals \( I = 400 \), and isolated individuals \( A = 400 \).

Figure 5.1 shows that the size of the acute care facility increases initially and then remains constant, which was expected as the hospital is at full capacity and the model was constrained. The size increases slightly from the initial size of 8,000 beds to 8,827 in the first two months, as the curve sometimes takes time to reach its stable state from the initial condition. The model results shown in Figure 5.2 indicates that the number of MRSA positive individuals identified on admission is fairly constant, with values ranging from 292 to 314 MRSA positive individuals identified per month. Similarly, the empirical data used for the model showed no increasing or decreasing trend in the number of people identified on admission.
The initial outputs measured for fitting the model were the number of individuals in each of the compartments in the acute care facility and in the community. Figures 5.3 and 5.4 show the number of individuals in the various compartments over the 24-month time period. The three compartments in the acute care facility: susceptible (S), unidentified-infected (I) and isolated (A) also remained relatively constant. The greatest numbers of individuals are classified as
susceptible. In the model the size of the S compartment increased from 7,200 to 8,537. Conversely the infected and isolated groups decreased from the initial state of 400 to 190 and 100, respectively.

In the community there are four compartments: susceptible-high-risk \( (S_{HR}) \), infected-high-risk \( (I_{HR}) \), susceptible-low-risk \( (S_{LR}) \), and infected-low-risk \( (I_{LR}) \). Figure 5.4 shows that the community compartments remain relatively constant. The susceptible-low-risk population represents the largest number of individuals at each time point, approximately 3.5 million individuals (not shown in Figure 5.4). The other susceptible compartment, for high-risk individuals, decreased slightly in the model from 340,000 to 310,615, and most of these individuals are then allocated to the susceptible-low-risk population. The susceptible high-risk compartment stabilizes after the 24-month period. The two infected compartments, high and low-risk did not change over the model period.

Figure 5.3: Distribution of Individuals in an Acute Care Facility by MRSA Status, by Month

In the community there are four compartments: susceptible-high-risk \( (S_{HR}) \), infected-high-risk \( (I_{HR}) \), susceptible-low-risk \( (S_{LR}) \), and infected-low-risk \( (I_{LR}) \). Figure 5.4 shows that the community compartments remain relatively constant. The susceptible-low-risk population represents the largest number of individuals at each time point, approximately 3.5 million individuals (not shown in Figure 5.4). The other susceptible compartment, for high-risk individuals, decreased slightly in the model from 340,000 to 310,615, and most of these individuals are then allocated to the susceptible-low-risk population. The susceptible high-risk compartment stabilizes after the 24-month period. The two infected compartments, high and low-risk did not change over the model period.
The least squares method used for parameter fitting found the optimal values for the hospital transmission ($\beta$) and community transmission parameter ($\varepsilon$), to be $0.0003677$ and $4.6221699 \times 10^{-7}$ respectively. The sum of squares (SS) for the two parameters that were used for fitting ($\beta$, $\varepsilon$, $d$, $r$, $q$) $SS=5.0117304910^8$ and for fitting ($\beta$, $\varepsilon$, $\rho_1$, $\rho_2$) $SS=4.70919 \times 10^{-8}$.

The Markov Chain Monte Carlo (MCMC) analysis returned a 95% confidence interval of $0.00021$ to $0.00041$ for the hospital transmission ($\beta$). The least squares fitting method found the point estimate of $\beta$ to be $0.000368$. The histogram in Figure 5.5 shows the probability distribution of $\beta$. It shows the normal distribution of $\beta$, with the peak slightly lower than the estimated point, but still aligned with the results from LHS and least squares analysis.

The 95% confidence interval for the community transmission parameter ($\varepsilon$), as determined by MCMC is: $1.56 \times 10^{-7}$ to $4.91 \times 10^{-7}$, with the point estimate after least squares fitting method $4.62 \times 10^{-7}$. Figure 5.6 shows the histogram of the probability distribution of $\varepsilon$. The distribution is skewed to values lower than the point estimate.
Figure 5.5: Probability Distribution of $\beta$ using MCMC.

Figure 5.6: Probability Distribution of $\varepsilon$ using MCMC.
Sensitivity analysis was conducted for hospital ($\beta$) and community transmission ($\epsilon$). LHS was used to generate 10,000 samples of these parameter values. The outcome for sensitivity analysis was the mean number of MRSA positive individuals identified on admission each year. For hospital transmission, sensitivity analysis showed that the mean number of MRSA positive individuals identified on admission was 3688.37 (approximately 307 per month), including new and previously known MRSA positive individuals (Figure 5.7). For the community transmission ($\epsilon$), the estimated mean number of MRSA positive individuals identified on admission each year was 3703.43 (approximately 309 per month), including new and previously known MRSA positive individuals (Figure 5.8). The model is sensitive to changes in the community transmission ($\epsilon$). There is only a small range of values of $\epsilon$ that are acceptable in the model.

Figure 5.7: Sensitivity Analysis for $\beta$ using LHS, Total MRSA Identified on Admission
Variations in Transmission

The fitted model outputs, after 24 months from the initial condition, are listed in tables 5.1-5.5. The tables show the number of isolated, infected, and susceptible individuals identified at month 24, as well as the number of MRSA positive individuals identified on admission. The cases identified on admission are those individuals admitted to hospital that are detected as MRSA positive at admission (i.e. people entering the isolated compartment). This outcome measure varies primarily depending on the screening rate.

Table 5.1 shows that as hospital transmission (β) decreases, the number of infected MRSA positive individuals that are hospital acquired or not identified on admission, those termed unidentified-infected (I), decreases. The initial fitted model had 190 unidentified-infected MRSA positive individuals. If β decreases by 50% then only 41 unidentified-infected MRSA positive individuals are present, a greater than fourfold decrease in cases. This shows that even at a very low transmission rate, some hospital acquired MRSA will occur. As β decreases so does the number of MRSA positive individuals identified on admission and these result in slightly smaller numbers of isolated MRSA positive individuals. Conversely, due to the
non-linear relationship between $\beta$ and unidentified-infected, as $\beta$ increases by 20% from the initial conditions the number of unidentified-infected MRSA positive individuals increases to 725.

**Table 5.1: Changing the Hospital Transmission Rate ($\beta$)**

<table>
<thead>
<tr>
<th>Transmission Parameter</th>
<th>Isolated (A)</th>
<th>Infected (I)</th>
<th>Susceptible (S)</th>
<th>Identified on Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreasing $\beta$</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ 10% $\beta$</td>
<td>65</td>
<td>116</td>
<td>8,646</td>
<td>253</td>
</tr>
<tr>
<td>↓ 20% $\beta$</td>
<td>59</td>
<td>81</td>
<td>8,686</td>
<td>233</td>
</tr>
<tr>
<td>↓ 30% $\beta$</td>
<td>56</td>
<td>61</td>
<td>8,709</td>
<td>220</td>
</tr>
<tr>
<td>↓ 40% $\beta$</td>
<td>55</td>
<td>50</td>
<td>8,724</td>
<td>212</td>
</tr>
<tr>
<td>↓ 50% $\beta$</td>
<td>54</td>
<td>41</td>
<td>8,734</td>
<td>206</td>
</tr>
<tr>
<td><strong>Increasing $\beta$</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ 10% $\beta$</td>
<td>95</td>
<td>366</td>
<td>8,366</td>
<td>372</td>
</tr>
<tr>
<td>↑ 20% $\beta$</td>
<td>135</td>
<td>725</td>
<td>7,966</td>
<td>530</td>
</tr>
<tr>
<td>↑ 30% $\beta$</td>
<td>189</td>
<td>1,191</td>
<td>7,447</td>
<td>740</td>
</tr>
<tr>
<td>↑ 40% $\beta$</td>
<td>242</td>
<td>1,640</td>
<td>6,945</td>
<td>949</td>
</tr>
<tr>
<td>↑ 50% $\beta$</td>
<td>288</td>
<td>2,041</td>
<td>6,497</td>
<td>1,132</td>
</tr>
</tbody>
</table>

*Baseline Model: (A) = 100, (I) = 190, (S) = 8,537, Identified on Admission = 292, $\beta$ = 0.000367716

Figure 5.1 shows the relationship between changing hospital transmission in the acute care facility and the effect on the compartments, I, A, and those MRSA positive individuals identified on admission. The initial model endpoint shown in Figures 5.9 and 5.10 are as follows: (A) = 100, (I) = 190, (S) = 8,537, and Identified on Admission = 292. The benefit of reducing hospital transmission is most significant for the first 20%, after which the number of isolated and unidentified-infected individuals plateaus. Conversely as $\beta$ increases there is a sharp increase in all three compartments (I, A, and those identified on admission). There is almost an exponential increase in the number of MRSA unidentified-infected individuals as $\beta$ increases more that 10% from the initial state, highlighting the fine balance that exists between hospital transmission and the three compartments.
Table 5.2 shows that as the community transmission ($\varepsilon$) increases so does the number of MRSA positive individuals identified on admission, the unidentified-infected MRSA positive individuals in the hospital, and the number of isolated MRSA positive individuals. When $\varepsilon$ is decreased by 50% the number of MRSA positive individuals identified on admission, unidentified-infected individuals (I) and isolated MRSA positive individuals (A) decreased to 60, 53 and 16 respectively from the initial values of 292, 190 and 100.
Table 5.2: Changing the Community Transmission Rate (ε)

<table>
<thead>
<tr>
<th>Transmission Parameter</th>
<th>Isolated (A)</th>
<th>Infected (I)</th>
<th>Susceptible (S)</th>
<th>Identified on Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Decreasing ε</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ 10% ε</td>
<td>55</td>
<td>148</td>
<td>8,624</td>
<td>214</td>
</tr>
<tr>
<td>↓ 20% ε</td>
<td>40</td>
<td>115</td>
<td>8,672</td>
<td>156</td>
</tr>
<tr>
<td>↓ 30% ε</td>
<td>29</td>
<td>89</td>
<td>8,709</td>
<td>114</td>
</tr>
<tr>
<td>↓ 40% ε</td>
<td>21</td>
<td>69</td>
<td>8,737</td>
<td>83</td>
</tr>
<tr>
<td>↓ 50% ε</td>
<td>16</td>
<td>53</td>
<td>8,759</td>
<td>60</td>
</tr>
<tr>
<td><strong>Increasing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ 10% ε</td>
<td>101</td>
<td>242</td>
<td>8,485</td>
<td>395</td>
</tr>
<tr>
<td>↑ 20% ε</td>
<td>136</td>
<td>303</td>
<td>8,388</td>
<td>530</td>
</tr>
<tr>
<td>↑ 30% ε</td>
<td>179</td>
<td>376</td>
<td>8,272</td>
<td>703</td>
</tr>
<tr>
<td>↑ 40% ε</td>
<td>234</td>
<td>458</td>
<td>8,135</td>
<td>918</td>
</tr>
<tr>
<td>↑ 50% ε</td>
<td>299</td>
<td>548</td>
<td>7,980</td>
<td>1,177</td>
</tr>
</tbody>
</table>

*Baseline Model: (A) = 100, (I) = 190, (S) = 8,537, Identified on Admission = 292, ε = 4.62*10^-7

The effect that the community transmission, ε, has on the number of MRSA positive individuals unidentified-infected in the hospital is less significant than the effect of changing the hospital transmission. In Figure 5.10 the changes in the community transmission (ε), can be seen to affect the three compartments (I, A, and identified on admission) in a similar manner as changes to the hospital transmission (β), but to a lesser extent than changes to β. Decreasing ε has a profound effect on the number of MRSA positive individuals identified on admission. This effect is greater than that seen with similar changes to β.
Table 5.3 shows that when both transmission parameters are changed, the effect on MRSA positive individuals in the hospital is compounded when both the hospital transmission ($\beta$) and the community transmission ($\varepsilon$) increase, even if the increases are small. The number of individuals in the infected compartment is primarily determined by $\beta$. The number of MRSA positive individuals identified on admission and isolated is most affected by changes in $\varepsilon$. Even a 5% decrease in $\beta$ and $\varepsilon$ reduces the isolated, infected and identified on admission MRSA positive individuals by 41%, 33% and 21% from the initial state. When both $\beta$ and $\varepsilon$ are increased by 10% the isolated, unidentified-infected and identified on admission MRSA positive
individuals increase by 25%, 128% and 67% respectively. The effect is most significant on the number of unidentified-infected patients in the facility.

### Table 5.3: Changing both Transmission Parameters

<table>
<thead>
<tr>
<th>Transmission Parameter</th>
<th>Isolated (A)</th>
<th>Infected (I)</th>
<th>Susceptible (S)</th>
<th>Identified on Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ 5% ε ↓ 5% β</td>
<td>59</td>
<td>128</td>
<td>8,640</td>
<td>230</td>
</tr>
<tr>
<td>↓ 10% ε ↓ 10% β</td>
<td>47</td>
<td>88</td>
<td>8,693</td>
<td>183</td>
</tr>
<tr>
<td>↑ 5% ε ↑ 5% β</td>
<td>96</td>
<td>288</td>
<td>8,443</td>
<td>376</td>
</tr>
<tr>
<td>↑ 10% ε ↑ 10% β</td>
<td>125</td>
<td>433</td>
<td>8,269</td>
<td>489</td>
</tr>
<tr>
<td>↑ 5% ε ↓ 5% β</td>
<td>80</td>
<td>166</td>
<td>8,580</td>
<td>315</td>
</tr>
<tr>
<td>↓ 5% ε ↑ 5% β</td>
<td>72</td>
<td>233</td>
<td>8,523</td>
<td>280</td>
</tr>
<tr>
<td>↑ 10% ε ↓ 10% β</td>
<td>89</td>
<td>153</td>
<td>8,585</td>
<td>347</td>
</tr>
<tr>
<td>↓ 10% ε ↑ 10% β</td>
<td>73</td>
<td>308</td>
<td>8,447</td>
<td>283</td>
</tr>
</tbody>
</table>

*Baseline Model: (A) = 100, (I) = 190, (S) = 8,537, Identified on Admission=292, β=0.000367716, ε =4.62*10^-7

### Variations in Screening

Changes to the admission screening also affect the number of MRSA positive individuals in each of the hospitalized compartments as shown in Table 5.4. As the proportion of high-risk patients screened on admission (α) increases, the initial number of MRSA positive individuals on admission increases but then levels off as there is a reduced number of MRSA positive individuals that are unidentified in the hospital that can transmit MRSA in the facility. Increasing α to 90% significantly decreases the infected compartment, while isolated MRSA positive individuals also decrease but by a lesser amount. The number of MRSA positive individuals identified on admission increases, as does the number of susceptible individuals. Changes to low-risk admission screening (δ) have a less pronounced effect than changes to α on the size of any of the hospitalized compartments.
Table 5.4: Changing the Admission Screening: High-risk screening (α) or Low-risk Screening (δ)

<table>
<thead>
<tr>
<th>Screening Parameter</th>
<th>Isolated (A)</th>
<th>Infected (I)</th>
<th>Susceptible (S)</th>
<th>Identified on Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>α =90%</td>
<td>85</td>
<td>63</td>
<td>8,680</td>
<td>331</td>
</tr>
<tr>
<td>α =80%</td>
<td>80</td>
<td>125</td>
<td>8,621</td>
<td>314</td>
</tr>
<tr>
<td>α =60%</td>
<td>68</td>
<td>256</td>
<td>8,503</td>
<td>263</td>
</tr>
<tr>
<td>α =50%</td>
<td>59</td>
<td>323</td>
<td>8,446</td>
<td>230</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Changing δ and α is constant at 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ = 0%</td>
</tr>
<tr>
<td>δ =20%</td>
</tr>
<tr>
<td>δ =30%</td>
</tr>
<tr>
<td>δ =40%</td>
</tr>
<tr>
<td>δ =50%</td>
</tr>
<tr>
<td>δ =60%</td>
</tr>
</tbody>
</table>

*Baseline Model: (A) = 100, (I) = 190, (S) =8,537, Identified on Admission=292, α=70%, δ=10%*

Table 5.5 shows what occurs in the hospital compartments when the admission screenings (α, δ) are made equal. The number of MRSA positive individuals identified on admission and those isolated increases with greater screening. The corresponding figure (Figure 5.11) shows the various relationships between admission screenings and the three key outcomes, number of MRSA positive individuals identified on admission, unidentified-infected and isolated. There is a linear relationship between infected and screening admission. There is nearly a ten-fold decrease in the number of infected individuals when screening is increased from 10% to 90% (Table 5.5).
Table 5.5: Changing both Admission Screening Levels

<table>
<thead>
<tr>
<th>Screening Parameter</th>
<th>Isolated (A)</th>
<th>Infected (I)</th>
<th>Susceptible (S)</th>
<th>Identified on Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>α, δ = 10%</td>
<td>14</td>
<td>586</td>
<td>8,226</td>
<td>57</td>
</tr>
<tr>
<td>α, δ = 20%</td>
<td>28</td>
<td>515</td>
<td>8,284</td>
<td>110</td>
</tr>
<tr>
<td>α, δ = 30%</td>
<td>40</td>
<td>444</td>
<td>8,343</td>
<td>158</td>
</tr>
<tr>
<td>α, δ = 40%</td>
<td>51</td>
<td>373</td>
<td>8,402</td>
<td>201</td>
</tr>
<tr>
<td>α, δ = 50%</td>
<td>61</td>
<td>305</td>
<td>8,461</td>
<td>239</td>
</tr>
<tr>
<td>α, δ = 60%</td>
<td>70</td>
<td>237</td>
<td>8,521</td>
<td>271</td>
</tr>
<tr>
<td>α, δ = 70%</td>
<td>76</td>
<td>173</td>
<td>8,579</td>
<td>297</td>
</tr>
<tr>
<td>α, δ = 80%</td>
<td>81</td>
<td>111</td>
<td>8,636</td>
<td>316</td>
</tr>
<tr>
<td>α, δ = 90%</td>
<td>85</td>
<td>53</td>
<td>8,690</td>
<td>329</td>
</tr>
</tbody>
</table>

(Universal Screening)

*Baseline Model: (A) = 100, (I) = 190, (S) = 8,537, Identified on Admission = 292, α = 70%, δ = 10%

Figure 5.11: Modeled Relationship between Admission Screening and Individuals who are Isolated, Infected and Identified on Admission in Acute Care facilities

When comparing the reduction in hospital transmission to an increase in screening as a mechanism by which to decrease MRSA in the hospital, a marginal (10%-20%) reduction in the hospital transmission rate decreases the MRSA infected individuals which in turn decreases the
isolated and identified on admission MRSA positive individuals. Alternatively, if screening increases then those identified on admission continues to increase and isolation is required for these individuals, but there is a reduction in HA-MRSA due to the reduction in unidentified-infected patients in the acute care facility.

**Specific Alberta Facilities**

*High Transmission-Hospital*

The average of two hospitals in Alberta, one in each of Edmonton and Calgary, was selected to determine how the model preforms under variety of conditions, and to estimate the hospital transmission ($\beta$) and community transmission ($\epsilon$) in these settings. Local data for hospital and population size were obtained in a similar manner to the initial model. These data were used to calculate the parameters as was done for the initial model.

**Table 5.6: High-risk Hospital Setting**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible in Hospital (S)</td>
<td>715</td>
</tr>
<tr>
<td>Unidentified Infected in Hospital (I)</td>
<td>50</td>
</tr>
<tr>
<td>Isolated in Hospital (A)</td>
<td>50</td>
</tr>
<tr>
<td>Susceptible High Risk ($S_{HR}$)</td>
<td>100,000</td>
</tr>
<tr>
<td>Infected High Risk ($I_{HR}$)</td>
<td>700</td>
</tr>
<tr>
<td>Susceptible Low Risk ($S_{LR}$)</td>
<td>2,000,000</td>
</tr>
<tr>
<td>Infected Low Risk ($I_{LR}$)</td>
<td>250</td>
</tr>
<tr>
<td>Admission rate for the low risk population ($\rho_1$)</td>
<td>2.733</td>
</tr>
<tr>
<td>Admission rate for the low risk population ($\rho_2$)</td>
<td>1.999</td>
</tr>
<tr>
<td>Hospital Transmission Rate ($\beta$)</td>
<td>0.000398858</td>
</tr>
<tr>
<td>Community Transmission Rate ($\epsilon$)</td>
<td>4.43422 x10^{-7}</td>
</tr>
<tr>
<td>Successful screening rate in high risk (HR) population ($\alpha$)</td>
<td>0.7</td>
</tr>
<tr>
<td>Successful screening rate in low risk (LR) population ($\delta$)</td>
<td>0.1</td>
</tr>
<tr>
<td>Discharge rate ($d$)</td>
<td>3.9443</td>
</tr>
<tr>
<td>The proportion of discharged individuals back to the low risk population from I ($r$)</td>
<td>0.559</td>
</tr>
<tr>
<td>The proportion discharged individuals back to the low risk population from S ($q$)</td>
<td>0.7435</td>
</tr>
</tbody>
</table>
Table 5.6 shows the parameter estimations from a high-risk hospital setting. The initial conditions were determined using the methods described above for the general model. The transmission, admission, and discharge parameters were fit in the same manner as the general model, with 100,000 simulations used to fit these parameters. Estimates for low and high-risk admission rates were nearly identical to the overall model estimates ($p_1=2.73$ vs. $2.9$ and $p_2=1.999$ vs. $1.403$), while the proportion of individuals discharged to the low-risk populations was different ($r=0.559$ vs. $0.647$), reflecting the higher hospital transmission parameter.

The hospital transmission rate is slightly higher than the general model while the community transmission rate is slightly lower. The general model is influenced by the large facilities in the province that were used for the higher hospital transmission scenario, and this accounts for the similar results found between the two scenarios. Figure 5.12 shows the MRSA identified on admission for the high transmission facility. The results are in line with the empirical data with which the model was used for fitting.

![Figure 5.12: MRSA Identified on Admission in High Hospital Transmission Setting](image)
The average of two hospitals in Northern Alberta was selected to determine how the model performs under a variety of conditions, and to estimate both the hospital ($\beta$) and community ($\epsilon$) transmissions. Table 5.7 shows the parameter estimations from a high-risk hospital setting. The initial conditions were determined using the methods described above for the general model. The transmission, admission, and discharge parameters were fit in the same manner as the general model, with 100,000 simulations used to fit these parameters.

**Table 5.7: High-risk Community Setting**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible in Hospital ($S$)</td>
<td>250</td>
</tr>
<tr>
<td>Unidentified Infected in Hospital ($I$)</td>
<td>3</td>
</tr>
<tr>
<td>Isolated in Hospital ($A$)</td>
<td>3</td>
</tr>
<tr>
<td>Susceptible High Risk ($S_{HR}$)</td>
<td>400</td>
</tr>
<tr>
<td>Infected High Risk ($I_{HR}$)</td>
<td>130</td>
</tr>
<tr>
<td>Susceptible Low Risk ($S_{LR}$)</td>
<td>350,000</td>
</tr>
<tr>
<td>Infected Low Risk ($I_{LR}$)</td>
<td>6</td>
</tr>
<tr>
<td>Admission rate for the low risk population ($\rho_1$)</td>
<td>2.99</td>
</tr>
<tr>
<td>Admission rate for the low risk population ($\rho_2$)</td>
<td>1.13</td>
</tr>
<tr>
<td>Hospital Transmission Rate ($\beta$)</td>
<td>0.00023539</td>
</tr>
<tr>
<td>Community Transmission Rate ($\epsilon$)</td>
<td>6.11705 x10-7</td>
</tr>
<tr>
<td>Successful screening rate in high risk (HR) population ($\alpha$)</td>
<td>0.7</td>
</tr>
<tr>
<td>Successful screening rate in low risk (LR) population ($\delta$)</td>
<td>0.1</td>
</tr>
<tr>
<td>Discharge rate ($d$)</td>
<td>3.181</td>
</tr>
<tr>
<td>The proportion of discharged individuals back to the low risk population from $I$ ($r$)</td>
<td>0.557</td>
</tr>
<tr>
<td>The proportion discharged individuals back to the low risk population from $S$ ($q$)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

The estimates for admission rates were nearly identical to the overall model estimates ($\rho_1=2.99$ vs. 2.9 and $\rho_2=1.13$ vs. 1.403). The transmission parameters were significantly lower for the hospital transmission ($\beta$) and about 1.5 times higher for the community transmission ($\epsilon$). Unfortunately constraining the hospital bed capacity to such a small facility size made the fitting of the parameters challenging. This was exacerbated by the small permissible values for the
community transmission parameter. Figure 5.13 shows the MRSA identified on admission for the low transmission facility with a high community transmission rate. The results are in line with the empirical data to which the model was fit.

![MRSA Identified on Admission](image)

**Figure 5.13: MRSA Identified on Admission in Low-Hospital Transmission Setting**

**Optimal Screening Levels**

Optimal screening is defined as the minimal number of people needed to be screened each month in order to reduce hospital acquired MRSA cases to the lowest possible number. Interactive sliders were developed to show the relationship between HA-MRSA cases and changes to either $\alpha$ (screening) or $\beta$ (transmission). Snapshots of specific screening levels are shown in the following Figures 5.14- 5.16. It is important to note that HA cases are cumulatively calculated in the month and while they might seem high, not all of the cases are in the hospital at any given time within the month. HA-MRSA represents a portion of the compartment of unidentified-infected (I) and is the result of hospital transmission of MRSA moving individuals from the susceptible compartment to the unidentified-infected (I) compartment.

The model shows that there is no achievable rate of admission screening that can reduce the number of HA to zero. Under current conditions, universal screening does reduce the number of
HA-MRSA cases to 151 after 24 months of screening, which is the lowest achievable level of HA-MRSA cases in the 24-month period (Figure 5.14). If the time period is extended and the community and hospital transmission rates remain stable then universal screening continues to decrease the number of HA-MRSA cases. At 36 months there are 121 HA-MRSA cases and at 48 months it is further reduced to 90 HA-MRSA cases. This represents a 40% decrease between 24 and 48 months of universal screening.

![Graph showing HA-MRSA cases per month with universal screening](image)

**Figure 5.14: HA-MRSA per month with Universal Screening**

An alternative approach to universal screening is targeted screening of the individuals at high-risk of MRSA. Figures 5.15a-f show the various patterns of HA-MRSA if the target screening rates are changed. The number of HA-MRSA cases increases over time with screening levels less than 45%. Screening 50% of the high-risk patients upon admission results in a constant number of HA-MRSA cases each month. If screening levels are increased above 50% of high-risk patients then the shape of the curve remains the same, however the number of HA-MRSA cases is reduced. Increasing the baseline screening (70% of high-risk patients) by
10% can reduce the MRSA cases by approximately 25% and when baseline screening is increased to 90% the reduction is greater than 50% from baseline. The lowest number of HA-MRSA cases is seen when 90% of the high-risk patients are screened upon admission. Screening at 90% results in fewer than 200 cases of HA-MRSA and as expected this is still greater than the number of HA-MRSA cases when all individuals are screened.

Figure 5.15a: HA-MRSA with 10% High-Risk Admission Screening
Figure 5.15b: HA-MRSA with 30% High-Risk Admission Screening

Figure 5.15c: HA-MRSA with 50% High-Risk Admission Screening
Figure 5.15d: HA-MRSA with 60% High-Risk Admission Screening

Figure 5.15e: HA-MRSA with 70% High-Risk Admission Screening
Figure 5.15f: HA-MRSA with 90% High-Risk Admission Screening

Rather than screening and isolation, it is possible to reduce the number of HA-MRSA cases by reducing the transmission within acute care facilities. Figure 15.16a-d shows the relationship between the hospital transmission rate and the number of HA-MRSA cases. As expected there is a decrease in the number of HA-MRSA cases when the transmission is reduced and an increase in the number of cases of HA-MRSA when the transmission is increased. A 20% decrease in the hospital transmission results in 137 cases of HA-MRSA after 24 months. When the hospital transmission rate increases to greater than 0.0004, this is a 20% increase, and the shape of the curve of HA-MRSA changes. A 30% increase in transmission (Figure 15.16d) would result in an outbreak situation as there would be thousands of HA-MRSA cases per month.
Figure 5.16a: HA-MRSA with a 20% Reduction in Hospital Transmission

Figure 5.16b: HA-MRSA with a 10% Reduction in Hospital Transmission
Figure 5.16c: HA-MRSA with a 20% Increase in Hospital Transmission

Figure 5.16d: HA-MRSA with a 30% Increase in Hospital Transmission
Reducing the hospital transmission of MRSA has the greatest effect on the burden of MRSA in acute care facilities in Alberta, including isolated and unidentified patients with MRSA. Admission screening also reduces MRSA in acute care facilities, but it is not as effective as reducing the transmission of MRSA.

**Summary of Findings**

The model shows that there is a reduction in HA-MRSA with either a reduction in MRSA transmission in the hospital or admission screening. The impact on HA-MRSA is greater with a reduction in the transmission in the hospital compared to screening.

Reducing the hospital transmission of MRSA leads to a decline in the number of individuals in the isolated, unidentified-infected and identified on admission category, while increasing the number of susceptible individuals in the hospital. The decrease in MRSA in the hospital is most apparent with the first 10-20% decrease in transmission. Conversely, an increase in the hospital transmission of MRSA rapidly increases the number of individuals that are unidentified-infected and identified on admission.

The community transmission parameter does not have the same effect on MRSA in the hospital as the hospital transmission parameter. The community transmission parameter has the greatest effect on the number of individuals who are identified on admission. However MRSA in the hospital is reduced with a decrease in the community transmission parameter.

Screening of more than 50% of admissions reduces unidentified-infected and increases the number of identified on admission and isolated patients. The impact of screening low-risk individuals is minimal. Screening of high-risk individuals has a bigger impact on MRSA in the hospital than low-risk screening.
Universal screening does not, after 24 months eliminate MRSA in the hospital. It does reduce the number of MRSA infected individuals to very low numbers. Screening of 90% of high-risk admissions has nearly the same effect as universal screening. HA-MRSA can be reduced with either screening or a reduction in MRSA transmission in the hospital.
CHAPTER 6

DISCUSSION

In this Chapter the results and the implications of the findings are discussed. The model findings and performance are assessed. Strategies to reduce MRSA in acute care facilities including screening are considered, and the results of the model compared to other studies. The strengths and limitations of the work are presented. Finally, possibilities for future work in this area of study are described.

Model Findings

The results of this Alberta model show that even under the maximum achievable screening levels of 90%, after a period of twenty-four months, MRSA cases still remain in the hospital. This indicates that universal screening and isolation alone will not eliminate MRSA in an acute care facility. This is because of ongoing admission to the hospital of some patients with MRSA and some, ideally minimal, level of ongoing transmission within the facility. If all patients with MRSA entering the facility could be identified and isolated, then there would no longer be hospital acquired MRSA. Unfortunately this is not an achievable option.

This Alberta model shows a targeted screening program for high-risk individuals with horizontal measures to reduce the hospital transmission rate is the most effective way to reduce MRSA in Alberta acute care facilities. The current baseline screening rate in Alberta of 70% of high-risk admissions, results in most of the MRSA colonized or infected individuals being identified and isolated. However screening of 90% of high-risk admission reduced the HA-MRSA cases by more than half and this in turn would reduce MRSA associated costs and poor patient outcomes. The decision to increase screening requires the cost of screening to be compared to the cost of the number of cases of MRSA averted and the prevention of outbreaks.
The model demonstrates the fine balance required for MRSA to persist in Alberta acute care facilities. Hospital transmission of MRSA alone is not sufficient to support an endemic state of MRSA in acute care facilities in Alberta. A constant influx of new patients with MRS entering the hospital is required. This is satisfied by new admissions of patients colonized with MRSA that are not identified on admission. If there are no new admissions of patients colonized or infected with MRSA that are not identified on admission, eventually there will be no more cases of MRSA in the hospital. This, however, is not possible as patients are readmitted while still colonized or infected. Additionally there is community acquired MRSA that can enter the hospital that is not eliminated with a reduction of MRSA transmission in the hospital setting. These newly admitted patients colonized or infected with MRSA are required to provide new sources of MRSA to maintain the transmission within the hospital.

An increase in hospital transmission of MRSA results in a sizeable increase in the number of colonized or infected (unidentified) MRSA patients. It also increases in the number of patients identified on admission to hospital. A hospital experiencing an epidemic likely has transmission rates of 20% or greater above baseline. That increase in the hospital transmission of 20% can be due to more patients with unidentified MRSA admitted or due to poor adherence to infection control policies.

The increase in the number of patients identified on admission that is associated with an increase in hospital transmission may seem counter intuitive, but literature suggests that a colonized or infected person has a 40% chance of readmission while still carrying MRSA\textsuperscript{170}. Patients colonized or infected with MRSA are leaving the hospital and then are readmitted while still colonized or infected with MRSA. This highlights the heterogeneous nature of the patient population and supports the decision to have both high and low-risk groups in the model.
The admission rate to acute care facilities in Alberta is higher for those at high-risk for MRSA either community or hospital acquired. It is this re-admission that makes targeted screening a great deal more effective than screening of all admitted individuals. Looking at two distinct patient populations allows screening policies and programs to be targeted to the appropriate group, in this case those who are re-admitted who are at high-risk of harbouring MRSA.

The model also shows that as hospital transmission decreases there is a diminishing return on investment. This is critical, so that IPC strategies that reduce MRSA transmission, either by identification of new MRSA cases and isolating them or by other measures, need not be perfect. Even a twenty per cent reduction in transmission of MRSA will reduce the number of infected and unidentified MRSA cases by half compared to baseline. A 10 to 20% reduction is likely achievable and staff and administration can see the benefit of the program. Ultimately, fewer people need to be screened and subsequently isolated if the transmission is reduced in the first place.

IPC strategies typically target hospital transmission of MRSA, yet community MRSA is a source of unidentified and unavoidable MRSA entering into acute care facilities. Alberta had a significant outbreak of community MRSA reported in 2005. This model showed that based on the empirical data, community transmission (ε) has a minor impact on the number of MRSA colonized or infected individuals entering a facility and an even lower impact on the number of unidentified-colonized or infected individuals with MRSA in the hospital. This is a non-linear relationship where if the community transmission parameter increases from the estimated current point in the model, there is a sharp increase in the number of MRSA colonized or infected individuals identified on admission and an increase in the infected compartment in the hospital.
However the effect on those not identified on admission or the absolute number of people in isolation is not as dramatic with increases in community transmission when compared to the effect of changes to the hospital transmission.

In the event of an MRSA outbreak in the community, it is important to remember the relationship between community transmission and the compartments in the model. As the model shows, there will be an increase in the proportion of those admitted with MRSA. During a community-based outbreak, altering the admission screening criteria should be considered to include even the low-risk individuals. Any group of individuals that are harbouring MRSA but who are not admitted but who are visiting or working at the facility may also alter the transmission dynamics of MRSA in the hospital. Screening both patients, staff, and visitors ought to be considered, especially in areas where there are higher rates of CA-MRSA. Any outbreak in the community or identified increase in community transmission should result in a reassessment of the current screening program. The model could be used to predict optimal screening in this circumstance.

**Model Performance**

This Alberta model, an ordinary differential equation compartmental model, performs well. The outputs produced by the manipulation of a variety of parameters, are within the range of values found in the literature and that produce realistic outputs. The hospital size remained fairly constant, as did the distribution of people within the compartments in the acute care facility. There was a decrease in the initial state for the unidentified and infected (compartment I) and isolated (compartment A) individuals. This is likely due to imperfect surveillance data and the manner in which the initial conditions are developed. However after the other parameters were fit and the transmission parameters calculated the model is able to produce the
expected results. The vast amount of surveillance data and point prevalence data coupled with infection control expertise in Alberta was an asset in the development of a representative, yet simple, model.

The overall fitting analysis, an indication of how precise the outcome points are, produced reasonable sum of squares and the estimated confidence intervals for both transmission parameters. The fitting results are reasonable. The estimate of the community transmission parameter was found to be much smaller than the hospital transmission parameter. Previous models have looked at a single hospital or ward specific transmission parameter and they are higher than the current model estimate\textsuperscript{129, 240, 241}.

There are two primary reasons for the higher transmission estimates in the literature. First, many of the models are based on the data and clinical practice in the United States. The epidemiology of MRSA in the United States is different than in Canada where the USA has consistently higher rates of hospital and community MRSA\textsuperscript{242, 243}. The admitting pattern and nature of a healthcare system has an influence on the epidemiology of diseases including MRSA.

Secondly, studies use the transmission rates in ICU and other wards. The ICU and other wards with very ill patients tend to have a higher prevalence of MRSA than the rest of the hospital and the ICU MRSA values are used as estimates of MRSA for studies\textsuperscript{244,245,246}. Many of the original mathematical models have used data from the ICU. This model, with its focus on admission screening when admitted to hospital would expect to have lower MRSA transmission parameters than in the ICU.

The sensitivity analysis shows the model is quite sensitive to changes in the community transmission parameter. There are two likely explanations for this. The first, is that the community transmission rate is so low that any increase would result in an epidemic state in both
the community and possibly the hospital. CA-MRSA is not known to be endemic in the general population in the developed world. The second is that this parameter was the one with the least empirical data with which to fit the parameter and there is an issue with non-identifiability. This could result in an estimate that is not accurate. However the fitting of multiple data sets, as an iterative process, makes this a less likely, but possible option.

This model fitted data using an iterative process, first with least squares, then Latin Hypercube Sampling (LHS) and Markov Chain Monte Carlo (MCMC) analysis\textsuperscript{247}. The use of both LHS and MCMC methods improves the understanding of the precision and importance of both the community and hospital transmission parameters and their estimated values for the model. These methods support the point estimates and the confidence interval that were obtained when the model was fitted. Using various types of fitting and fitting more than one parameter at one time ensures that estimated parameters reflect closely across various model outcomes and minimizes non-identifiability issues.

The model was used in two scenarios, one with a low rate of HA-MRSA transmission and one with a higher rate, as compared to the provincial average. The model performed well in the higher transmission setting due to at least two key factors. First, both the hospital and population size is large enough to support the type of compartment model used. Second, the hospital transmission is sufficient to provide outcome measures that are similar to the overall provincial model and to the specific hospitals themselves. The model can now be used for these higher transmission settings to assess various admission screening scenarios and interventions that effect the transmission of MRSA in that specific acute care facility.
The model was not successful in predicting the behaviour of low-risk settings. The characteristic that determined the success of the model in predicting high-risk settings were responsible for its failure in low-risk settings. The hospitals that are considered low-risk have fewer beds, a smaller catchment population, virtually no hospital transmission of MRSA and possibility HA-MRSA cases are missed if there are fewer resources for IPC surveillance in these facilities.

The two hospitals used for the low-risk setting do have higher incidence of MRSA in the community than the rest of Alberta. This results in fitting values for the community transmission parameter that was higher than the general Alberta model, but did not translate into higher proportions of unidentified-infected or isolated individuals. This supports the conclusion that community transmission of MRSA is less important than hospital transmission of MRSA for reducing MRSA in the hospital setting.

For facilities with small bed numbers and low prevalence of transmission, agent-based or stochastic models offer a better opportunity to model the chance events in the population or individual variations that are important when dealing with small populations.

Using a stochastic or agent based model would be ideal in an ICU or small acute care facility as small numbers and acts of chance influence the model outcome. Recently, modeling of MRSA transmission has used agent-based modeling\textsuperscript{229}. In this agent-based model, each patient is identified on admission as being colonized or not, has a projected length of stay and a degree to which they are susceptible to colonization. Development of this type of model would better identify MRSA transmission dynamics in low-transmission acute care facilities in Alberta.
Admission Screening to Reduce MRSA

Admission screening for MRSA was the intervention that the model assessed. Each of the groups of individuals at high and low-risk for acquiring MRSA had screening parameters that were manipulated to find the best screening strategy for Alberta acute care facilities. The screening of low-risk individuals has a minimal impact on the MRSA transmission dynamics in the hospital. An increase in screening of low-risk patients may not be justified if the patients are required to be isolated until proven negative or simply due to the increased cost of laboratory testing\textsuperscript{248,249}.

Universal screening in the Alberta model assumes a maximum of ninety per cent of admitted patients can be screened as practically no system is perfect. This is supported by a Canadian research study that found that universal screening captured less than 85\% of admitted patients\textsuperscript{250}. In other studies the rate of universal screening has been closer to the ninety per cent as well\textsuperscript{251,252}.

The model shows screening of less than 50\% of high-risk patients can lead to almost 20\% of hospitalized patients with an MRSA infection or colonization. The optimal screening rate for high-risk admissions is between 70\% and 90\%. This results in the lowest number of HA-MRSA cases, assuming no other changes in practices that would reduce transmission of MRSA in an acute care facility including decolonization, rapid screening or changes in horizontal measures such as hand hygiene. The ideal strategy includes screening of high-risk individuals combined with other measures to reduce the transmission and the reservoir of MRSA in the hospital population.

If those individuals that are missed for admission screening are different from those who are screened, this may represent a significant problem, as this would introduce selection bias.
The data collected on those that are screened will continue to feed the information loop for screening criteria and the assessment of who is colonized or infected with MRSA on admission. If there is a selection bias as a result of not screening certain groups of high-risk patients then there is reduced effectiveness of screening and screening tools and models will be built with incorrect information.

It is important to quantify the local epidemiology and risk factors that are needed to develop prediction tools used for MRSA screening. This model used data from Alberta to enable the development of a more robust model. Looking at the demographic and selected characteristics of all patients that are admitted to an acute care facility and not simply those who test positive on admission is important. Understanding the local risk group data with risk group specific denominators is important to understand how the local situation compares to the literature. Then, finally, a screening tool can be developed to target those at highest risk of harbouring MRSA on admission.

There is a linear relationship between admission screening and unidentified-infected individuals in the hospital. As screening increases, there is a decrease in the number of unidentified-infected individuals. However, as screening increases there are more individuals identified on admission who will subsequently require isolation. While the model has infinite isolation capacity, this is not the reality in most acute care facilities. The utility of isolation is limited by capacity.

In order to reduce the burden of MRSA within a facility, either through reducing transmission or improving screening, the screening must be tied to an action. In the model the action is isolation. This has classically been the strategy to reduce MRSA transmission in acute
care facilities. However, this action does not eliminate the MRSA it simply reduces transmission in the hospital setting.

In the model, isolation was considered perfect. Isolation is not perfect; however, isolation with screening has been associated with a decrease in MRSA\(^{254}\). In some settings, isolation or cohorting of MRSA-positive patients did not reduce cross infection\(^{113}\). Healthcare workers may not be compliant for the contact precautions required for entry into, or exit from, an of an isolation room. Appropriate barrier precautions instead of patient isolation have also been shown to be comparable in reducing disease transmission\(^{255}\). In Alberta acute care facilities it would be interesting to determine how effective isolation is at reducing MRSA transmission. These data could then be incorporated into the model.

The greater the initial transmission rate in a facility, the more effective isolation and other measures appear to be at reducing rates of MRSA. This model was developed based on a low prevalence setting and isolation might be even less than 50% effective based on the literature. This is a concern as the value in screening and identifying patients with MRSA lies in the action to which the screening is tied. The use of isolation as part of a strategy to reduce MRSA transmission must consider the capacity of the facility for isolation, the compliance rate among healthcare workers and the negative effects experienced by patients as a result of their isolation.

Screening is often combined with either isolation and possibly also decolonization, as this both identifies those with MRSA and then attempts to reduce the transmission and the reservoir. Universal decolonization strategies to reduce MRSA, such as daily chlorhexidine bathing for all patients, are most effective in high prevalence settings\(^{124,125}\). Epidemiological studies have provided good information on the efficacy of decolonization. This, in turn, allows models to
determine that even at low rates of efficacy, decolonization works better than isolation to reduce MRSA in the hospital\textsuperscript{122}.

Decolonization has the benefit of not only reducing MRSA but other organisms as well. Chlorhexidine reduces MRSA on the skin and also prevents the growth of other organisms as well as MRSA resulting in decreased invasive infections including CVC-BSIs. Hand hygiene and decolonization are effective against a variety of organisms. Consideration of the patient population is critical when considering the merit of decolonization, with or without screening. This is important when considering the various costs of interventions.

This model did not consider decolonization in order to reduce the transmission of MRSA. The efficacy of decolonization in the Alberta acute care setting would need to be assessed. Specifically in order to consider including it in a model, it would be necessary to know the likelihood of completion prior to discharge and other issues, such as cost, which can impact use of decolonization.

**Alternative Strategies to Reduce MRSA**

The model shows that reducing hospital transmission is more efficient than increasing screening. Consideration needs to be made for other non-screening options that decrease antimicrobial resistant organism (ARO) transmission, with upstream measures to decrease transmission better than simply identifying the issue. Improving antibiotic stewardship and improving hand hygiene compliance are horizontal measures that have been shown to reduce MRSA and other healthcare associated infections.

This model does not specifically look at antimicrobial stewardship and there is limited literature on the association between reducing antimicrobial use in the hospital and the rates of MRSA. Generally, a reduction in antimicrobial load is important to decrease antimicrobial
resistance. Appropriate use of antibiotics including: macrolides, cephalosporins, amoxicillin-clavulanate, clindamycin and fluoroquinolones in conjunction with other measures are correlated with a reduction in specific HA-MRSA strains. Studies exploring the association between antibiotics and MRSA in the hospital setting have been cross-sectional and ecological. Further study in the area is required.

For decades, proper hand hygiene has been associated with a decrease in HA-MRSA. A recent methodologically sound, quasi-experimental study supports the use of hand hygiene as the most effective way to decrease MRSA in acute care facilities. However the intervention included decolonization. Some debate exists about whether the reduction in MRSA was attributable to the improved hand hygiene.

Other studies report that a high rate of hand hygiene compliance is associated with a reduction of MRSA in the hospital. Hand hygiene compliance of over 75% is difficult to achieve, and can be highly variable between facilities. Fortunately in Alberta the rates of hand hygiene have increased from when the model was developed. The provincial compliance rate in 2014 was reported as 73% an increase from only a 50% compliance rate in 2011. The range of hand hygiene compliance in Alberta is quite good. The geographic zone with the lowest reported rate of hand hygiene compliance was 67%. If hand hygiene levels stay above 70%, there should be a decrease in HA-MRSA in Alberta.

Bundling is another strategy to reduce MRSA transmission in hospitals. Bundling has been effective in reducing healthcare associated infections including catheter-associated bloodstream infections (CVC-BSI) in ICUs. It has been met with variable success in other areas of acute care. Although it is part of recommendations in the United States, the evidence to support surgical site infection bundle is mixed and has not significantly reduced
There is limited evidence to support the cost of the bundle but it may be considered in a high prevalence setting. Jain et al., found that screening and isolation to be effective as part of a bundle, resulting in a 62% reduction of healthcare-associated MRSA\textsuperscript{179}. Furthermore this reduction was sustained for three years\textsuperscript{274}. In infection control this is no small accomplishment. Bundles that include chlorhexidine baths and hand hygiene are effective at reducing the prevalence of MRSA without screening\textsuperscript{275}.

Bundled approaches have the strength that they are multifaceted and target the reservoir and the transmission. They often include horizontal measures that can reduce other AROs as well as the target organism. However, disentangling the contribution of each of the bundle components can be difficult. Elements of the bundle could be removed without negative consequences, but without evidence for the contribution of each element the bundle must be delivered as a whole.

A systematic literature review that assessed screening, decolonization and isolation concluded that there is no one-size-fits-all strategy to reduce MRSA, as the effectiveness of the strategy is so highly associated with the prevalence and transmission rate of MRSA in the hospital and the general IPC measures in the hospital\textsuperscript{276}. Based on the nature of MRSA in Alberta, and these model findings, the best technique for reducing MRSA in the hospital is combining targeted screening with other strategies known to reduce transmission and the reservoir of MRSA in acute care facilities.

**Comparison to other Studies**

The Alberta model provides results that are similar to other international modeling. Other mathematical models have shown that screening with isolation, with or without decolonization, can be an effective tool to decrease the prevalence of MRSA in acute care
However, other models have shown that alternative MRSA control strategies are more effective at reducing MRSA \(^{226,277,278}\). The modeling group from the Netherlands, which includes Drs Bootsma and Bonten, have produced the most compelling arguments in favour of high-risk screening and subsequent isolation and decolonization. The stochastic models they have developed are very similar to the Alberta model, in terms of the parameters, assumptions and results. The recent work by this group found that universal screening is not as effective as targeted screening, especially in low prevalence settings\(^ {133}\). These findings are in line with the Alberta model results.

This model has similar findings to other studies that found that control measures may have both direct effects on HA-MRSA in the hospital and also an indirect effect through readmissions; the fewer HA-MRSA cases, fewer individuals will be colonized when readmitted to the hospital\(^ {167}\). Reducing the reservoir ensures that controlling spread of the nosocomial MRSA will become easier over time.

Models have determined that a non-screening strategy, hand hygiene, is effective at reducing MRSA \(^{124,129,260}\). Both decolonization and hand hygiene reduce the transmission of MRSA in the hospital, with decolonization also decreasing the reservoir. These findings are also in line with the Alberta model that shows a targeted screening program with horizontal measures to reduce the hospital transmission rate is the most effective way to reduce MRSA in Alberta acute care facilities.

The only other published Canadian model used a Monte Carlo simulation model rather than a dynamic transmission model\(^ {279}\). It assessed the effectiveness of screening, nurse to patient ratios, and hand hygiene and found that the most effective strategy for reducing the rate of
MRSA transmission was high hand hygiene compliance. This model used similar parameters, patient population and healthcare system.

This is the first Canadian model to use transmission rather than a series of probabilities to look at the screening and the transmission of MRSA in acute care facilities. This model can be used in other Canadian settings and can be modified to look at other aspects of MRSA transmission in the hospital either in Alberta or elsewhere in Canada.

This Alberta model is unique as it has low prevalence of MRSA in the facility and in the community compared to models from many other countries. Although European rates of MRSA are decreasing, in many countries the rate of MRSA remains higher than in Canada\textsuperscript{280,281,282,283}. Data used for many models even in settings that have seen a decrease in MRSA rates, used data from the high prevalence period to build the model\textsuperscript{284}. The only models with comparable prevalence of MRSA are the more recent models from the Netherlands.

One reason for the low prevalence in the Alberta model is that the entire hospital population was included. This includes low-risk areas of the hospital, such as maternity and psychiatry. However this was necessary as it was important to assess screening of the whole patient population. Even in low-risk units such as psychiatry, transmission of MRSA can occur\textsuperscript{285}.

In addition to the low prevalence of MRSA, this modeling activity is unique due to the setting of the model, the large amount of data, the time period of the model results, and compartments in the model. The Alberta healthcare system has a single acute care provider. This setting is unique in the world and allows for many facilities to have equivalent protocols and procedures.
Infection control policies and practices are standardized provincially and this provides surveillance data that is of exceptional quality for research, including modeling. Often in model development, researchers use published data from a variety of non-standardized sources and this can result in inaccuracies in the model. One of the unique aspects of this model is the quality and consistency of the surveillance data used.

Finally, the time period of the model is much shorter than many other models. This is important in order to make the model relevant. The model is intended for screening strategies to reduce MRSA in the current acute care setting. Strategies that are effective only in reducing MRSA in ten to twenty years are not practical or useful.

**Generalizability**

This model is well suited to be used in other Canadian provinces. The nature of the model is such that if most of the parameters are approximately the same the model results for Alberta can be applied. Local data for admission and discharge data, as well as the number of MRSA positive people that are identified on admission can be used by other jurisdictions to assess the suitability of the model. If the numbers align with Alberta’s then no further adjustments are required. If there are differences, particularly in the number of MRSA positive people, then the model would need to be re-fitted with the new data. The structure of the model would remain the same.

In order to use the model in other countries refitting of the model, based on the local data, is likely required. It is necessary to understand the nature of the healthcare system and barriers to access the system that may vary between individuals with and without MRSA. A healthcare setting with very high endemic rates of MRSA transmission will require the model to be re-fitted.
Strengths and Limitations

The Alberta model has some limitations and areas that could be improved. The most significant limitation was that isolation was modeled as perfect. In fact, isolation is not perfect. The model shows that reducing transmission has a greater effect on MRSA in the hospital than screening and isolation. Improving isolation for patients with MRSA should be a priority to support the current screening program that is in the model.

Another limitation is that the transmission rates of different MRSA strains may not be the same in the hospital. CA-MRSA strains may have a higher likelihood of causing infection. By their nature infections are more obvious and dramatic and these factors likely result in better infection control measures taken by healthcare workers when compared to colonized individuals. Healthcare workers interacting with patients have variable ability to spread MRSA in the hospital.

Some patients, via the hands of healthcare workers, are known to be much more effective at transmitting MRSA. This is due to mobility, failure to comply with treatment or isolation and other factors. These “super spreaders” are likely to change the dynamics of the model\textsuperscript{266}. The development of an agent based model could be used to investigate both how characteristics of individual patients and strains of MRSA impact the transmission dynamics of MRSA in the hospital.

Many of the unique qualities of the model are also the strengths of the model. As previously noted the ability to fit the model to a variety of empirical data is highly unusual in mathematical modeling. The nature of MRSA in Canada, with similar healthcare delivery and lower rates of HA-MRSA than in the United States, allows this model to be used in other Canadian provinces with minimal modifications.
Another of the strengths of the model is the community and hospital feedback loop related to admission and discharge of infected patients. Patients are discharged to the community and then interact in their respective population risk groups. The feedback loop provides some of the evidence to support additional mechanisms to reduce MRSA transmission and even strategies such as decolonization to reduce the number of MRSA carriers which in turn reduces transmission as well.

This feedback loop is critical, as much of the MRSA re-entering the hospital could have been acquired while in hospital. People in Alberta are likely to return to the same hospital and this does impact screening positivity rates. This community feedback provides a more realistic model that displays the transmission dynamics of MRSA in Alberta.

**Future Work**

While this model provides the foundation to expand or develop new models for the Canadian context, there remains work that should be undertaken. The addition of the costs and cost-effectiveness would be beneficial. The collection of further epidemiological data, particularly in the community is advantageous for fitting and refining the model. Finally, the development of an agent-based model would greatly increase the evidence to support a strategy to decrease MRSA in the hospital.

Economic modeling was not explicitly part of the modeling for this work, but it is important to understand the costs associated with MRSA reduction strategies including: screening, isolation, decolonization or hand hygiene. The Alberta model shows that universal screening will not eliminate MRSA from acute care facilities in Alberta. Additionally, studies have found that universal screening and rapid testing are not cost-effective in low prevalence settings such as Alberta\(^{287,288}\).
A review by Farbman et al., found that in general, savings were seven times higher than the costs associated with any infection control intervention and there are more cost-savings in high prevalence settings\textsuperscript{289}. There is imprecision to cost analysis and the availability of cost data may be limited. These factors need to be considered along with practical and ethical issues before deciding on the best course of MRSA reduction in a specific facility or region.

Further investigation and data on prevalence of MRSA in the community and in sub-populations within the general community would assist in the refinement of the current model. A point prevalence and risk survey would be useful to determine if there are unknown groups at higher risk for MRSA. If necessary, the model could then be a re-fitted or an additional compartment added to incorporate this new information.

Finally, the development of an agent based model to explore in depth individual interactions in the healthcare setting would be a significant accomplishment and an asset to infection control planning in Alberta. An agent-based model could allow for additional details to be incorporated into the model. This could include looking at different units in acute care, patient characteristics, and visitors in acute care, and healthcare worker behaviours. The Alberta model lays the foundation for the development of an agent-based model.

**Conclusion**

This is a new era where mathematicians and epidemiologists each contribute and provide evidence to improve healthcare planning and patient safety. There has been an evolution from simple models to complex models, using epidemiologic data to evaluate the models and inform the current models that better represent current healthcare systems.

Based on the local epidemiology used to develop this model, the conclusions drawn from the model are that targeted screening will reduce unidentified infected MRSA positive
individuals. However, reducing hospital transmission is more effective at reducing MRSA in the hospital. In order to reduce the transmission of MRSA, a risk assessment should be considered, with the risks of each strategy considered. A made in Alberta solution that considers factors such as the baseline hand hygiene compliance, the prevalence of MRSA and other microorganisms in the facility, staff culture and behaviour and the size of the facility is required.
REFERENCES


10 IPC Director, Elizabeth Henderson, Alberta Health Services Personal Communication (August 20, 2015)


15 McKinnell JA, Miller LG, Eells SJ, Cui E, Huang SS A systematic literature review and meta-analysis of factors associated with methicillin-resistant Staphylococcus aureus colonization at time of hospital or intensive care unit admission. Infection Control and Hospital Epidemiology. 2013;34(10):1077-86.


Vidal PM, Trindade PA, Garcia TO, Pacheco RL, Costa SF, Reinert C, Hiramatsu K, Mamizuka EM, Garcia CP, Levin AS. Differences between “classical” risk factors for infections caused by methicillin-resistant Staphylococcus aureus (MRSA) and risk factors for nosocomial
bloodstream infections caused by multiple clones of the staphylococcal cassette chromosome mec type IV MRSA strain. *Infection Control and Hospital Epidemiology*. 2009;30(2):139-45.


117 Kypraios T, O'Neill PD, Huang SS, Rifs-Shiman SL, Cooper BS. Assessing the role of undetected colonization and isolation precautions in reducing methicillin-resistant


128 Beggs CB, Shepherd SJ, Kerr KG. How does healthcare worker hand hygiene behaviour impact upon the transmission of MRSA between patients?: an analysis using a Monte Carlo model. *BMC Infectious Disease*. 2009;9:64.


133


270 Weber DJ, Brown VM, Sickbert-Bennett EE, Rutala WA. Sustained and prolonged reduction in central line-associated bloodstream infections as a result of multiple interventions. *Infection Control and Hospital Epidemiology*. 2010; 31: 875–877


141