Modeling Methicillin-Resistant *Staphylococcus Aureus* Spread and Progression among Exposed Roommates in Canadian Hospitals

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

The control of Methicillin-resistant Staphylococcus aureus (MRSA) has been a controversial issue worldwide. In Canada, the incidence of MRSA among admitted patients has been increased steadily from 0.44 cases per 1,000 patient admissions in 1995 to 9.5 per 1,000 patient admissions in 2009. Screening and isolating exposed roommates of an MRSA carrier is recommended by Provincial Infectious Diseases Advisory Committee; however, the optimal screening strategy including the sampling time and the screening method still remains uncertain. This uncertainty makes it difficult to determine cost-effective isolation duration for the roommates and may result in increased cost, prolonged isolation time, and lowered quality of life for the isolated patients.

In order to balance between the potential harms and benefits of reducing the isolation duration, a simulation approach has been established to model MRSA spread and progression among the exposed roommates by using data from the literature and Canadian hospitals. After the unknown parameters have been estimated from the model calibration, the calibrated model is transformed in comparing the following main policies: Policy 1) 7-day isolation and administering culture tests at day 0 and day 6, which is the existing policy in Grand River Hospital and St Mary's General Hospital; Policy 2) 3-day isolation and administrating a culture test at day 0 and a PCR test at day 3, which is the proposed policy to be tested by simulation. Our numerical results show that under the baseline assumptions Policy 2 provides significantly shorter isolation time, dramatically lower total cost, and slightly less colonized and missed cases than those from Policy 1. In addition, extensive sensitivity analyses are conducted which illustrate that this conclusion is valid unless the transmission probability during isolation is extremely low. Furthermore, additional analysis is conducted to measure the robustness of our results to the violation of some of the disease progression assumptions.

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I wish to thank Doctor William Ciccotelli for his support as a clinical expert. He provided valuable data from the hospital and the constructive feedback from his professional perspective which helped us develop a realistic model.

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Chapter 1

Introduction

Since 1995 Methicillin-resistant Staphylococcus aureus (MRSA) became a reportable disease in Canada, the number of MRSA cases increased from 189 in 1995 to 6,646 in 2009 (CNISP, 2011), which was a nearly 35-fold increase in the 15 years. Additional health care required by MRSA management is imposing enormous financial burden on the health care system (Kim et al., 2001). Moreover, MRSA infection is associated with increased mortality incidence as serious MRSA infections such as bacteremia is often life-threatening; Pastagia et al. (2012) reported that the mortality rate of bacteremia was 31.5%. Multifaceted interventions have been recommended to control MRSA spread including hand hygiene, active surveillance screening, contact precautions, environmental cleaning, and decolonization. Provincial Infectious Diseases Advisory Committee (PIDAC, 2013) suggests targeted screening based on risk factors for MRSA carriage in professional health care settings in Ontario, Canada. One of the particularly high risk factors has been defined as previously exposed to an MRSA carrier. Ontario Medical Association (2010) reported that 93% of Ontario hospitals isolate and screen the exposed roommates; however, the optimal screening time, methods, and isolation duration for the roommates remain uncertain (Ng et al., 2012).

In Grand River Hospital and St. Mary's General Hospital (GRH & SMH), the exposed roommates are isolated in the same patient room for 7 days during which culture-based MRSA screening tests are administered at post-exposure day 0 and 6. Meanwhile, the initial carrier is transferred to an MRSA-positive room immediately, and the bed previously occupied by the patient will be empty until isolation ends. Roommates who are tested with positive result during isolation will be moved to the MRSA-positive room as well. At the end of isolation, all roommates will be released. However, patients who were tested with false negative (the missed cases) will cause a new cycle of contact precautions. Figure 1.1 illustrates the process of MRSA management among the exposed-roommates on a simplified example.

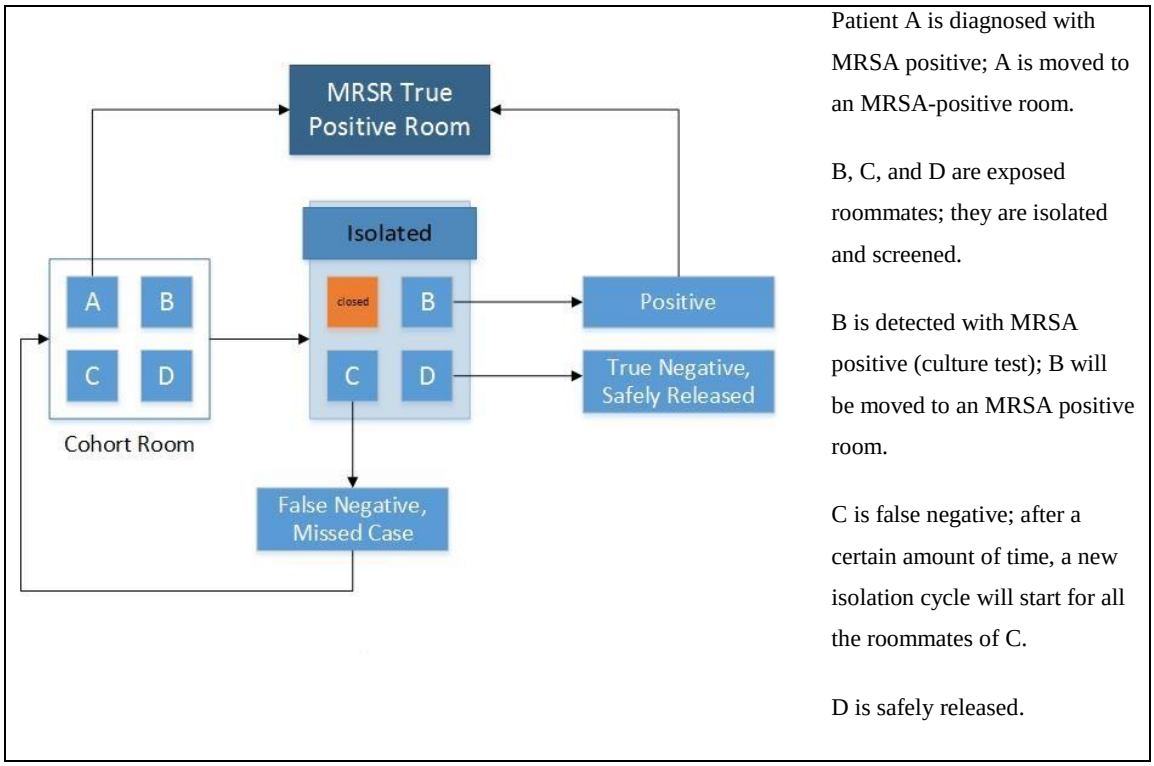

Figure 1.1: Sample process flow for the management of exposed-roommates

1.1 Motivation

Since low colonization density due to insufficient incubation could lead to false negative results (PIDAC, 2013), enforcing longer isolation allows more incubation time and higher probability for detecting an unknown carrier. However, as the total number of MRSA cases increase annually, the costs and resources involved in managing MRSA will increase correspondently. Moreover, distinguishing between the colonized and the non-colonized is difficult; i.e., isolating the non-colonized patients is unnecessary but inevitable. Therefore, reducing the unnecessary isolation is clinically and economically desirable. Nevertheless, mistakenly releasing the colonized ones will be risky to other patients in the absence of isolation.

Polisena et al. (2011) reported that shorter turnaround time of PCR screening accelerated MRSA detection. Ng et al. (2012) found that PCR sensitivity at post-exposure day 3 was similar to that of culture at day 7, and they mentioned that the accelerated detection may reduce the empirical isolation duration. Based on the previous findings, this study will evaluate the impact of implementing shorter isolation and PCR screening compared to the conventional approach for managing the exposed roommates. Specifically, a simulation model is developed and applied to

compare the performances of the following policies in the Grand River Hospital: i) 7 day isolation and administering culture tests at day 0 and 6; ii) 3 day isolation and administrating a culture test at day 0 and a PCR test at day 3; iii) 7 day isolation and administering culture tests at day 6 only; and iv) 3 day isolation and administering PCR tests at day 3 only. The main performance measures include the following:

(1) the number of colonized cases;
(2) the number of missed (false negative) cases;
(3) the number of new transmitted cases during isolation;
(4) the cost of implementing MRSA regulation for exposed roommates within a year.

1.2 Current MRSA status in Canada

1.2.1 What is MRSA?

MRSA is a type of staph bacteria which is resistant to multi-antibiotics. In healthcare settings, MRSA can cause life-threatening infection such as bloodstream infections, pneumonia, and surgical site infections (CDC, 2006). MRSA can be either healthcare associated (HA-MRSA) or community associated (CA-MRSA); i.e., HA-MRSA is related to colonization and transmission in healthcare facilities. The disease can spread via the direct contact to an MRSA case or the contaminated hands of a health care worker. Evidence shows that some patients may act as "super-shedders" of MRSA who are co-infected with respiratory virus that can spread MRSA through respiratory droplets (PIDAC, 2013).

1.2.2 MRSA incidence

CNISP (2011) reported that MRSA incidence had been increasing gradually but continuously, from 0.44 per 1000 patient-admissions in 1995 to 9.5 per 1000 patient-admissions in 2009 in Canada. Figure 2.1 shows the increasing trend of MRSA cases in Canada.

Regional distribution of MRSA was reported to have an increasing trend in the east, center, and west part of Canada. The center (Ontario and Quebec) area had the highest number of colonized cases with 3,176 in 2009, while the east part (New Brunswick, Newfoundland & Labrador, and Nova Scotia) had the largest number of infections with 961 in the same year. PIDAC reported that 19,962 patients were identified with MRSA colonized or infected in Ontario (2011) and the number of MRSA bacteraemia was 560, which was a 13% increase over the number in 2010.

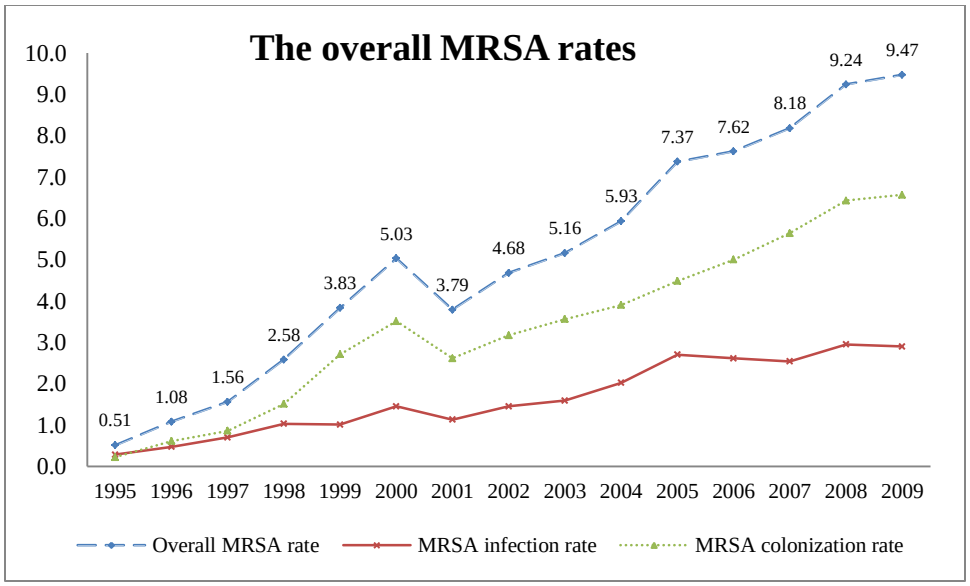

Figure 1.2: Overall MRSA rates from 1995 to 2009 (CNISP, 2011)

1.2.3 Economic impact of MRSA in Canada

MRSA infection or colonization is usually associated with high costs. The colonization was estimated to be $5,235.14 CAD/patient (Giuseppe et al., 1999), which included the costs of an isolation room, isolation gowns and gloves, medications, follow-up screenings, and recommended infection control measures. Kim et al. (2001) evaluated the colonization cost to be widely ranging from $58 to $13,940 with a mean of $1,363. Meanwhile, they determined the cost of an infection to be $14,360 and estimated the total cost associated with MRSA in Canadian hospitals to be $42 million to $59 million annually. However, the infection cost is closely affected by the treatment methods for which the average cost is estimated $7,693 and $8,444 for patients treated with linezolid and vancomycin, respectively (Rosner et al., 2004).

1.3 Guidelines for MRSA screening and isolation

MRSA screening practices may significantly vary among hospitals. Ontario Medical Association reported that 21% of hospitals in Ontario implemented MRSA screening for all admissions, and the majority of hospitals (187 out of 201) screened exposed roommates. According to Ontario guideline (PIDAC, 2013), professional health care facilities are expected to screen the patients, clients, and residents at increased risk for MRSA acquisition. Meanwhile contact precautions may be instituted for patients who have particular high risks of being MRSA colonization or infection before their screening results become available. The risk factors include:

(1) previously identified with MRSA infection or colonization;
(2) previously received health care in another country;
(3) roommates of patients or residents who are newly identified as MRSA positive;
(4) previously spent more than 12 hours in a hospital setting in the past 12 month;
(5) exposed to patients or residents on a ward or unit with an MRSA outbreak;
(6) household contacts of persons known to be colonized or infected with MRSA
(7) patients with skin and/or soft tissue infections in areas where the prevalence of CA-MRSA is high or increasing

Exposed roommates, as contact patients who share the same room, ward, procedure or health care provider with an identified MRSA case, should have at least two follow-up screenings, with one taken at a minimum time of seven days after the last exposure to the identified carrier, and preemptive isolation may be instituted before their screening results reported.

Active surveillance screening and contact precautions are also suggested in the United States. According to Centers for Disease Control and Prevention (CDC), patients who are identified with MRSA colonization or infection or who are suspected with MRSA colonization should be applied with contact isolation and assigned with the single rooms with the highest priority. When single rooms are not available, place the MRSA patients in a cohort room with appropriate semi-isolation treatments. However, the duration of contact precautions is not well defined, since the re-occurrence of MRSA carriage has been frequently reported after the initial clearance (CDC, 2006).

1.4 Structure of thesis

In Chapter 2, a comprehensive literature review is listed and discussed. While Chapter 3 describes the data collection and processing as well as the model for parameter estimation, Chapter 4 presents the policy evaluation model which utilizes the parameters from Chapter 3 to compare the existing and the proposed policy, respectively. In Chapter 4, the significance of T1 screening is evaluated as well. Then, Chapter 5 reports a robustness analysis by relaxing the assumption that all MRSA colonization cases are detectable. With this relaxation, the correlation between the consecutive screening results is incorporated into the model by using which we evaluated the impact of screening at day 1, 2, 3 …, or 6. Chapter 6 shows the results of the policy evaluation with sensitivity analysis conducted on the input-output transformations. Chapter 7 discusses the

results obtained from the previous chapter and analyzes the limitation of the research. Finally, Chapter 8 draws the conclusion.

To the best of our knowledge, this is the first study that proposed a natural history model for MRSA progression and spread among the exposed roommates considering the impact of the missed cases and the risk of isolating the roommates individually and collectively. By using the data from the existing clinical literature and Grand River Hospital & St. Mary's General Hospital, as well as adopting the expert advice from Dr. William Ciccotelli, the simulation model is calibrated and validated iteratively so that it imitates the system as realistic as possible.

Results show that the early detection of PCR with shortened isolation is dominantly preferable in terms of minimizing total cost and the number of newly transmitted cases throughout all possible transmission probabilities and screening sensitivities. However, the number of the colonized cases and the missed cases are just slightly reduced when culture day 6 screening is replaced by PCR day 3 screening under the base case scenario. Therefore, intensive sensitivity analyses are conducted conditionally on the baseline assumptions to examine under which combination of transmission probability and screening sensitivity PCR is inferior or superior to culture in saving the number of the colonized and the missed cases. It is concluded that early detection through PCR testing at day 3 (Policy 2) reduces the number of colonized and missed cases, and the cost under aggressive MRSA transmission. On the other hand, culture test at day 6 (Policy 1) could be better if the transmission is not aggressive and sensitivity of culture test is high enough.

Chapter 2

Literature Review

Multi-faceted interventions have been implemented in MRSA control. This review chapter will firstly focus on the studies associated with active surveillance screening (universal admission screening and targeted screening) and contact precautions. In the second section, previous stochastic models on the topic of MRSA spread and progression are presented and discussed.

2.1 Control measures of MRSA

2.1.1 Universal admission screening

Universal screening requires all admissions screened. Robicsek et al. (2006) examined the effectiveness of universal admission screening in 3 affiliated hospitals. The control interventions included PCR screening for MRSA, topical decolonization therapy, and contact precautions for positive cases. Results showed that universal admission screening was associated with a reduced prevalence density of MRSA infection.

Lee et al. (2010) constructed a stochastic computer simulation model to determine the potential economic impact of performing universal screening. Meanwhile, patients with positive results were placed under contact precautions. It was reported that based on the quality adjusted life year equals $50,000 (USD) per year, universal admission screening could be cost-effective when the prevalence level was no less than 1% and the reproductive rate was 0.25 or higher. Three benchmarks statistics were provided under which universal screening would be the dominant strategy. These statistics can help the decision makers to determine the optimal strategies according to their local prevailing conditions.

However, the value of universal screening has always been a controversial issue. PIDAC (2013) mentioned the following:

> "Though some studies indicate that universal/admission screening may be cost-effective, other evidence suggests that targeted screening has similar sensitivity to universal

screening and that it may be an effective strategy when combined with other control measures, particularly in non-critical settings." (p.7)

Therefore, the following contents in Section 2.1 will highly stress on the alternative screening strategy – targeted screening.

2.1.2 Targeted screening based on risk factors

Instead of screening all admissions, the practice of screening patients or health care workers who have the increased risk(s) of MRSA acquisition is called targeted screening.

Harbarth et al. (2006) identified nine independent risk factors of MRSA acquisition, which incorporated male sex, age higher than 75 years, previous exposure to fluoroquinolones in the past 6 months, urinary catheter at admission, intra-hospital transfer etc. It is suggested that applying control measures to the newly admitted patients based on the risk factors above would improve the control efficiency when the prevalence of previously unknown MRSA was high. Rodrı´guez-Ban ˜o et al. (2010) evaluated the long term effectiveness of implementing successive targeted screening for MRSA carriers. Preemptive isolation was placed for patients previously colonized with MRSA. The study found that screening the patients and the health care workers in specific wards according to the priorities (specified by analyzing the clinical epidemiology data) would provide a significant reduction in MRSA incidence.

CDC (2006) recommended follow-up culture screenings base on certain risk factors for MRSA colonization, which include antibiotic exposure, exposure MRSA colonized patients or prolonged hospitalization in a high risk unit. PIDAC (2013) identified definite risk factors for MRSA acquisition, such as previously colonized or infected with MRSA; spent more than 12 hours in any health care facility in the past 12 months; recently exposed to unit or area of a health care facility having an MRSA outbreak; and received health care in another country.

2.1.2.1 The screening time for exposed roommates

MRSA detection is difficult since the incubation time of MRSA is uncertain. Evison and Muhlemann (2008) evaluated a double screening strategy for detecting MRSA carriers among patients who had pre-exposed to an MRSA carrier; preemptive isolation was placed for these patients. They found that screening an exposed patient too shortly after his or her last exposure might lead to a false negative result because the colonization process might include an incubation period during which the screening result would remain negative due to the low density level.

Therefore, they estimated the incubation time to be 5-11 days when screened with culture method. In addition, the study mentioned that applying a more sensitive screening method might be able to find a shorter incubation time.

Ng et al. (2012) addressed the incubation property by introducing the terminology of conversion, which was defined as a patient who had no MRSA history and had a negative test result on admission but was subsequently tested positive during the follow-up screening. The study suggested that PCR testing at post-exposure day 3 (55%) has similar performance to culture at day 7 (56%) in detecting the number of MRSA conversions. Combined with the shorter turnaround time (the time between the sample collected from the patient and the screening result reported) of PCR, the similarity of the sensitivities enlightens the attractive idea of whether it is possible to reduce the isolation duration and the time of second screening from 7 days to 3 days.

The uncertain conversion time was also reported by Moore et al. (2008). The study clarified that among 198 exposed roommates who had complete follow-up screening, 25 of them were found MRSA positive. Specifically, 10 of the 25 positives were detectable at the first screening (day 1), and 5 out of the 25 became positive at the second screening (day 4-6). From day 7 to 10, another 10 cases became conversions. However, for the remaining 2 positive cases, one was identified at post-exposure day 16 and the other was found at day 18.

Harbarth et al. (2003) evaluated PCR screening and preemptive contact isolation for detecting MRSA patients in critical care. The median time for identifying the previous unknown patients had been reduced from 4 days to 1 day when PCR was applied. And the rapid screening method was associated with significant lower number of cross-infections. In addition, the median time interval from admission to the first MRSA positive culture result was reported to be 5 days (range: 2 - 22 days).

Literature implicates that the incubation time of MRSA is ranging from 1 to 22 days when culture test is applied, and screening the exposed roommates too shortly after the last exposure is highly possible to cause more missed cases. This is consistent with the results shown in CDC (2006), which mentioned that the reoccurrence of MRSA is frequent after the initial clearance. However, since the resources involved in contact precautions are demanding and the longer isolation duration would also result in more unnecessary isolation days for non-colonized patients, the study attempts to capture cost-effective isolation duration in MRSA control.

2.1.2.2 Screening methods

Two categorized methods are implemented for MRSA detection – culture based and PCR based. The performances of culture and PCR have been evaluated in multiple studies. Polisena et al. (2011) conducted a systematic review on the clinical effectiveness of rapid tests for MRSA. They summarized eleven previous studies and suggested that patients screened with PCR were less likely to spread MRSA in hospitals compared with patients tested with culture. The study reported a significant shorter turnaround time of PCR versus that of culture test. The turnaround time is shown in Table 2.1.

Table 2.1: Turnaround time of PCR (type specified) and culture tests from several studies

Study	PCR based method		Culture based method
	PCR (BD GeneOhm)	PCR (Xpert)	Chromagenic agar
Laurent, 2010	-	1.9 hours	66.9 hours
Creamer, 2010	-	17.1 hours	53.9 hours
Hardy, 2010	21.6 hours	-	55.2 hours
Snyder, 2010	17.4 hours (positive results)	-	28.1 hours (positive results)
	14.4 hours (negative results)	-	51.3 hours (negative results)
Aldeyab, 2009	19.3 hours (positive results)	-	51.8 hours (positive results)
	22.7 hours (negative results)	-	42.2 hours (negative results)
Jeyaratnam, 2008r	21.8 hours	-	46.4 hours

The screening sensitivity and the specificity are two main factors in evaluating the performances of a screening method. When both PCR and culture are conducted on a previously known carrier, PCR has higher sensitivity than culture while the specificity of PCR is lower than that of culture; the lower specificity usually results in more false positives. Therefore, culture tests are required to confirm the positive results from PCR tests (PIDAC). Blanc et al. (2010) reported high proportion of wrongly identified MRSA carriers by using PCR; they reported that PCR did not directly target on the mecA gene but the SCCmec within the chromosome, and some SCC element that did not contain mecA gene would lead to the false positives.

Tübbicke et al. (2012) concluded that PCR sensitivity varied widely from 62.5% to 100% with mean of 91.09% among the general patient group, while the sensitivity of culture test among the general admissions ranged from 53.0% to 100% with mean of 89.01%; PCR sensitivity was consistently higher than culture sensitivity in each individual study. Drews et al. (2006) found an increase in PCR sensitivity when samples were taken from multi-sites of MRSA carriers.

Note that all the sensitivity values above were calculated based on the MRSA known cases. These sensitivity values are not directly applicable to the exposed roommates since the carriers among the roommates are previously unknown; instead, the sensitivity from Ng et al. (2012) should be applied as this value incorporated the impact of MRSA incubation.

2.1.3 Contact precautions and transmission probability

Active surveillance screening is usually applied with the combination of contact precautions. Center of Disease Control (CDC) recommends "contact precautions when the facility (based on national or local regulations) deems MRSA to be of special clinical and epidemiologic significance". Several studies show that contact precautions result in reduced number of MRSA transmissions.

Jernigan et al. (1996) evaluated the effectiveness of isolation during an MRSA outbreak when weekly culture screenings were insisted in the hospital. The study reported a significant lower transmission rate for patients in isolation (0.009 transmissions per day) than the rate for those who were not in isolation (0.140 transmissions per day). Bracco et al. (2007) used the retrospective data to compare the rate of MRSA transmission among patients in single and bay rooms. The reported incidence was 1.3 per 1000 patient days for patients in single rooms and 4.1 per 1000 patient days for patients in bay rooms. Data suggested that in an institute where MRSA is not hyper-endemic, single rooms might help to reduce nosocomial infection and cross transmission. Cheng et al. (2010) introduced the sequential single room isolation and hand hygiene campaign in an intensive care unit (ICU), a significantly decreased MRSA infection rate was reported in this study.

2.1.4 The counterpoint of contact precautions

Although contact precautions have been reported effective in several studies, one study stated that precautions were not effective in their unit where MRSA is not endemic (Cepeda et al., 2005). During the one year study, patients who were tested with positives or had noticeable pathogens were moved to other single rooms or cohort bays; no evidence showed that moving positive patients out would reduce cross-infection. However, Tacconelli (2012) pointed the limitations of the former study: the small sample size involved in the study and the long turnaround time of culture screening (4 days) during which the transmission between patients could happen with high probability.

In addition to the higher cost involved, patients under isolation were more likely to have depression and anxiety. Lower hospital satisfaction was also reported from the patients under contact precautions (Morgan, 2009). Similarly, Stelfox et al. (2003) examined the safety of patients under infection control. The study found that under contact isolation patients were more likely to have preventable adverse events, express dissatisfaction of health care, and have less documentable health care.

The advantages and the disadvantages of the contact precautions raised the frequently debating question of whether it is necessary to conduct contact precautions. However, judicious implementation of the intervention is required and should be tailored to the circumstances of the health care settings.

2.2 Stochastic models on MRSA spread and progression

Compared to the deterministic approaches, stochastic approaches are capable of analyzing the uncertainty involved in clinical decision processes. Stochastic models including decision trees, simulations, and mathematical models have been introduced in search of better MRSA management. Note that the generalized categorizations below are not necessarily exclusive from one to the other.

2.2.1 Decision tree approach

Decision trees are frequently used in costs comparison and cost-effective analyses in MRSA management which usually aim to find a better combination among multi-faceted interventions.

Brown et al. (2010) applied a decision tree to evaluate the effectiveness of PCR screening on the mortality rate and on the cost-effectiveness of patients with bactereamia. They concluded that PCR testing would potentially reduce the mortality rate and costs than the culture screening under a wide range of MRSA prevalence and PCR implement costs.

Nelson et al. (2010) developed a decision analysis model and conducted Monte Carlo simulation to perform a cost-effective analysis on adding decolonization therapy to patients screened and isolated for MRSA. It was reported that adding decolonization to the active surveillance strategies would reduce the number of infections and mortalities, as well as the average cost of a patient compared with the performances of active surveillance screening alone or no interventions.

Tübbicke et al. (2013) utilized a decision tree to compare the expected costs associated with different MRSA screening and management strategies. Decision factors included the screening scope (universal screening or targeted screening), methods (PCR or culture), contact precautions (with or without preemptive isolation) as well as culture confirmation (whether or not to confirm a PCR positive result). They found that targeted screening with PCR and followed by a culture confirmation for the high risk patients plus preemptive isolation would provide the lowest costs in a hospital. The decision tree is shown in Figure 2.1.

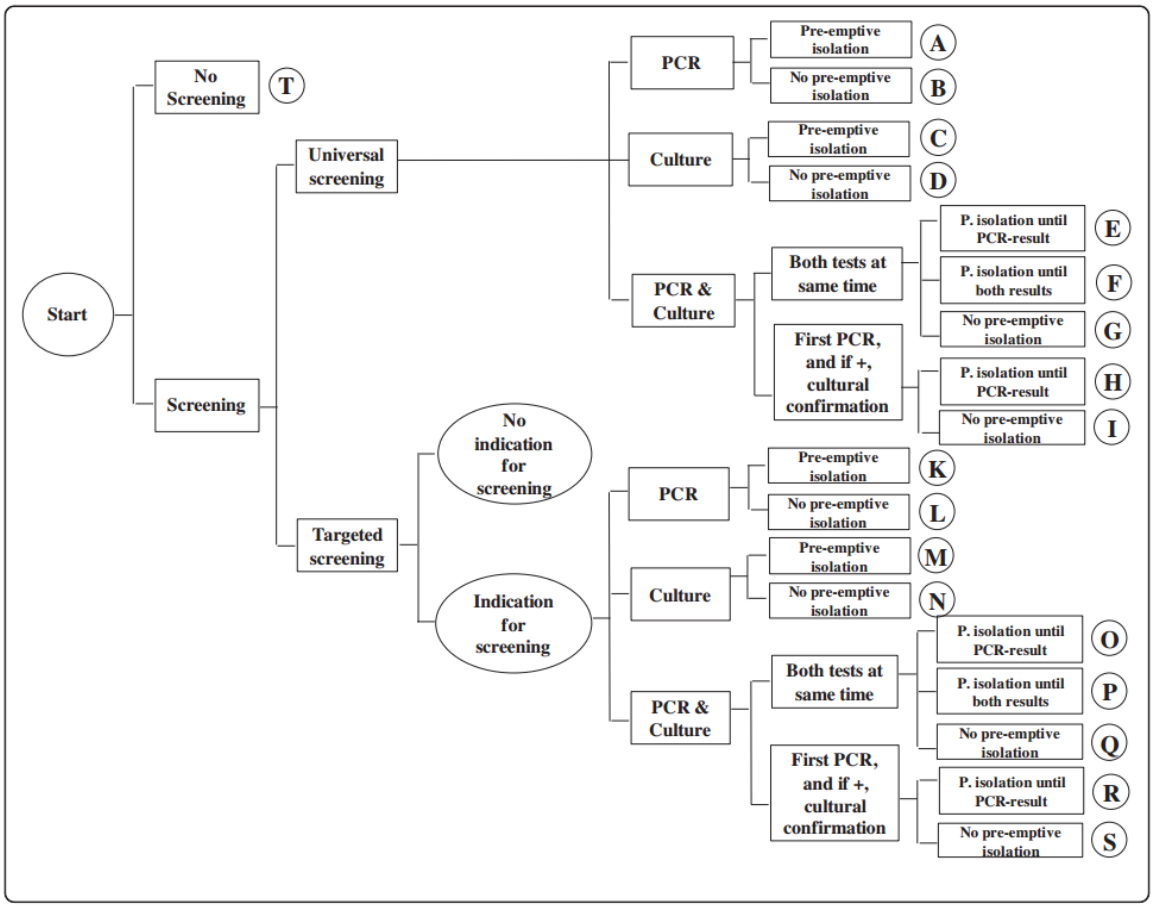

Figure 2.1: Decision Tree of the cost comparison (Tübbicke et al., 2013)

2.2.2 Simulation models

Simulation models are generally used when the system of interest is large and complex. Raboud et al. (2003) conducted a Monte Carlo simulation in modeling MRSA spread in a hospital, within which MRSA positive patients were placed in contact isolation. They reported the transmission rates to be 0.00081 per day for patients in isolation and 0.0137 per day for patients not in isolation.

Nyman et al. (2011) defined a patient's MRSA status as "no MRSA infection or colonization", "MRSA colonization", "MRSA infection 1", "MRSA infection 2", "discharge", and "death". "MRSA Infection 1" was defined as a temporary state which referred to the first day of MRSA infection. They developed a Markov simulation model and considered all the possible transitions from one state to the other. It was reported that screening of ICU patients and isolating colonized cases can save money due to reduced number of infections. The MRSA transition process is shown in Figure 2.2.

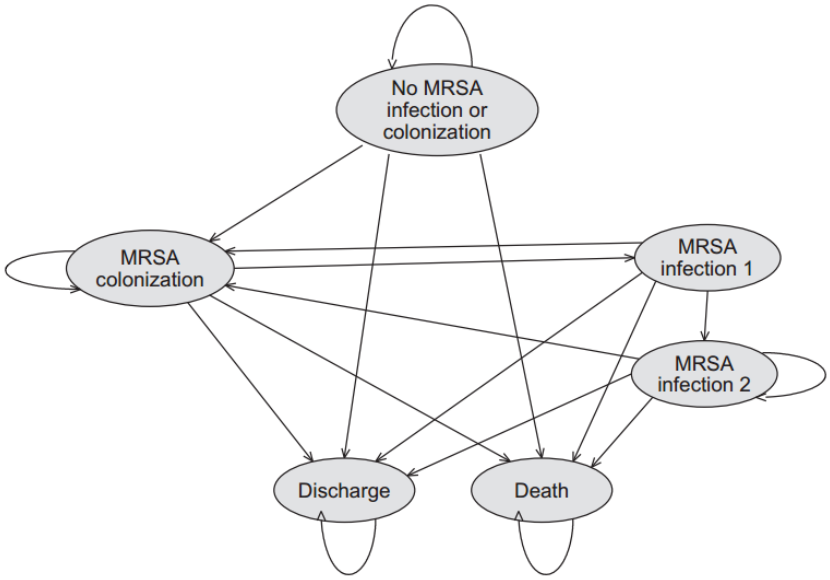

Figure 2.2: The transition process from one MRSA state to another (Nyman et al., 2011)

Lee et al. (2011) examined the economic impact of screening haemodialysis (HD) patients for MRSA by applying a Markov computer simulation model. Similar disease status were defined as "Not colonized", "Colonized no infection", "Infection with outpatient treatment", "infection with inpatient treatment" and "Death". The transition probabilities were time-dependent and adjusted based on the local prevalence. Results suggested that periodic testing with the HD patients for MRSA with culture or PCR would provide cost-effective outcomes under a wide range of MRSA prevalence level, decolonization costs, and decolonization success rates.

2.2.3 Mathematical stochastic models

Mathematical approaches were also introduced in modeling MRSA transmission and progression. Forrester et al. (2005) applied a statistical model to estimate MRSA transmission rates in three different sources – background contamination, non-isolated inpatients, and isolated inpatients.

They found that the rate of background source transmission to be 0.0092 (95% CI, 0.0062-0.0126) case per day; the number of transmissions among non-isolated inpatients to be 0.0052 (95% CI, 0.0013-0.0096) case per day; and the figure of isolated patients to be 0.0015 (95% CI, 0.0001-0.0043) case per day.

2.3 A summary of literature review

Literature review shows massive number of studies analyzing the effectiveness of multi-faceted MRSA control interventions. However, how to best implement active surveillance screening and contact precautions remains controversial.

(1) Preference of universal screening or targeted screening has been the most frequently discussed question; however, there is no decisive conclusion on which one is superior.
(2) Since the incubation time of MRSA is uncertain, deciding the optimal screening time is not an easy task. Earlier detection might cause more missed cases, while later detection might cause more transmitted patients.
(3) Culture test has lower sensitivity (when it is applied at the same time as PCR) and longer turnaround time than those of PCR. However, the former has higher specificity and is usually required in confirming PCR positive results. In addition, PCR is more expensive.
(4) The necessity of applying preemptive isolation and the duration of the contact precautions (for both preemptive and non-preemptive isolation) have not been well defined in literature. Similar to the second consideration, the uncertainty of incubation time and the relationship between the colonization level and screening sensitivity makes it difficult to decide a proper duration.

Moreover, existing studies directly associated with the topic of exposed roommates are limited. Studies focusing on the screening time, method, and isolation duration for roommates are even less. In addition, no simulation model has ever been built to find the cost-effective time of screening the isolated roommates. Our simulation model is established to evaluate the screening policies on the exposed roommates directly. Specifically, the model incorporates varying screening sensitivities of culture and PCR at different screening times.

Chapter 3

Parameter Estimation Model

A simulation approach is applied to compare the performances of different policies in Grand River Hospital and St. Mary's General Hospital. However, this comparison requires derivation of several unknown parameters, such as the transmission probability of in-isolation and not-in-isolation, and screening sensitivity at day 0(Culture), 3(PCR), and 6(Culture). Therefore, we first developed a parameter estimation model to derive these unknown parameters in Chapter 3 based on the observational data in North York General Hospital, ON-Canada (Ng et al., 2012). We base our input analysis primarily to the data provided in Ng et al. (2012) because 1) it is representative of Canadian hospital setting; 2) it is one of the few studies (the one with the largest sample space) that compared the PCR testing in the middle of the isolation and culture testing at the end of the isolation period.

Based on the results from the paper (Ng et al., 2012) titled as "Too close for comfort: Screening strategy to detect methicillin-resistant Staphylococcus aureus conversion in exposed roommates", the estimation model first utilizes the observational statistics in the paper as benchmark statistics and then calibrates the unknown probabilities so that the estimation model's results match well to these benchmark statistics. The benchmark statistics are as follows:

the proportion of conversions detected at T1 (day 0-1) is 30% by culture test;
the proportion of conversions detected at T2 (day 2-4) is 55% by PCR test;
the proportion of conversions detected at T3 (day 5-10) is 56% by culture test;
the overall conversion rate is 8% of the total roommates.

In Chapter 4, the estimated parameters will be the input parameters of the policy-evaluation models. Conclusions will be made based on the comparison results.

3.1 The study from North York General Hospital

The parameter-estimation model is established based on the situation of North York General Hospital. It is reported that 842 exposed roommates were isolated and screened from June 2005 to December 2010. 557 of them were screened with culture at T1. 225 and 442 patients were tested

by PCR and culture at T2, respectively. In T3, 397 roommates had culture tests. Figure 3.1 shows the screening sequence of the roommates. The study reported that 55% of the conversions were detected in T2 with PCR and the rate in T3 with culture was 56%. It was concluded that PCR sensitivity at day 3 was similar to that of culture at day 7.

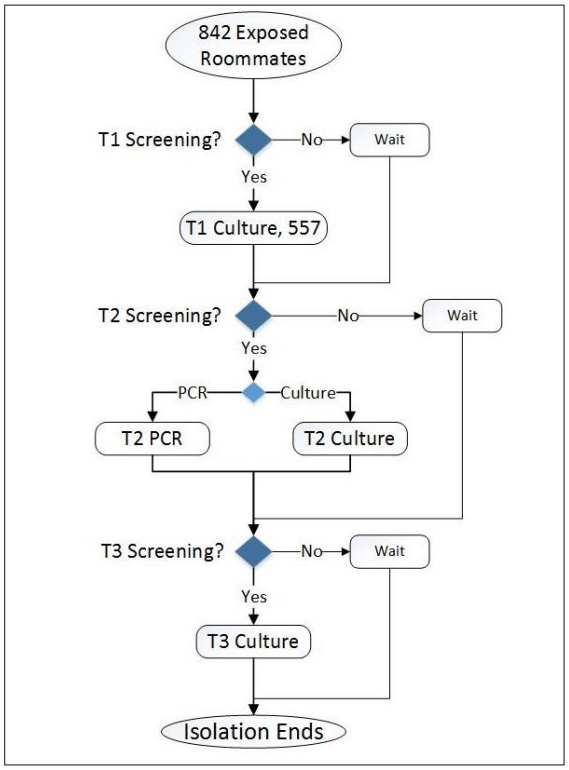

Figure 3.1: The screening sequence of the 842 exposed roommates

However, the 55% were the total numbers from day 2, 3, and 4. Likewise, the 56% were from day 5 to 10 altogether. Simply concluded that PCR (day 3) sensitivity is 55% and culture (day 7) sensitivity is 56% could be problematic. For instance, if most positives are found at day 2 and day 3 by PCR tests and most positive cases are detected at day 8 to 10 by culture tests, then the similarity of the screening performance would be challenged: PCR will be more sensitive than culture. On the contrary, if most positives detected by PCR are at day 4, and most of the positives detected by culture are at day 5 to 7; then, PCR sensitivity will be even less than the that of culture. Moreover, between day 2-4 and 5-10 new colonization cases may emerge due to the MRSA spread.

The study ignored transmission between screenings among the exposed roommates. However, given the fact that 70% rooms are multi-bed rooms, the in-isolation transmission probabilities are

likely to be greater than 0; therefore, the transmission element shall not be ignored. We incorporated the transmission element in the estimation model by making certain assumptions for objective assessment of PCR and culture sensitivities.

3.2 The conceptual model and assumptions

3.2.1 The conceptual model

The conceptual model shown in Figure 3.2 demonstrates the main components and concepts of the systems. Entities arrive in the system as the initial exposed or the missed generated roommates are placed in isolation. In terms of attributes: patients are categorized as non-colonized, colonized, and infected. In terms of activities: patients undergo culture or PCR tests, and moved to MRSA positive room. For the events and state variables: patients arrive and depart the system frequently and transmissions among them happen occasionally, the numbers of patients with different MRSA status change correspondently. Table 3.1 shows the summarized information of the system.

Table 3.1: Main components of the system

Components	Interpretation
System	Isolation and screening management system
Entities	Initial exposed roommates, *missed-case generated roommates
Attributes	Non-colonized, colonized, infected
Activities	PCR test, culture test, culture confirmation test
Events	Arrivals (isolation starts), departures (isolation ends)
State Variables	Number of non-colonized, colonized, detected, and infected patients from each patient room; number of missed cases, the room size, etc.

* Missed generated roommates refer to those who were exposed to a missed case from precious isolation procedure.

A missed case is a patient who did not have any positive result from T1 to T3 but later found to be positive.

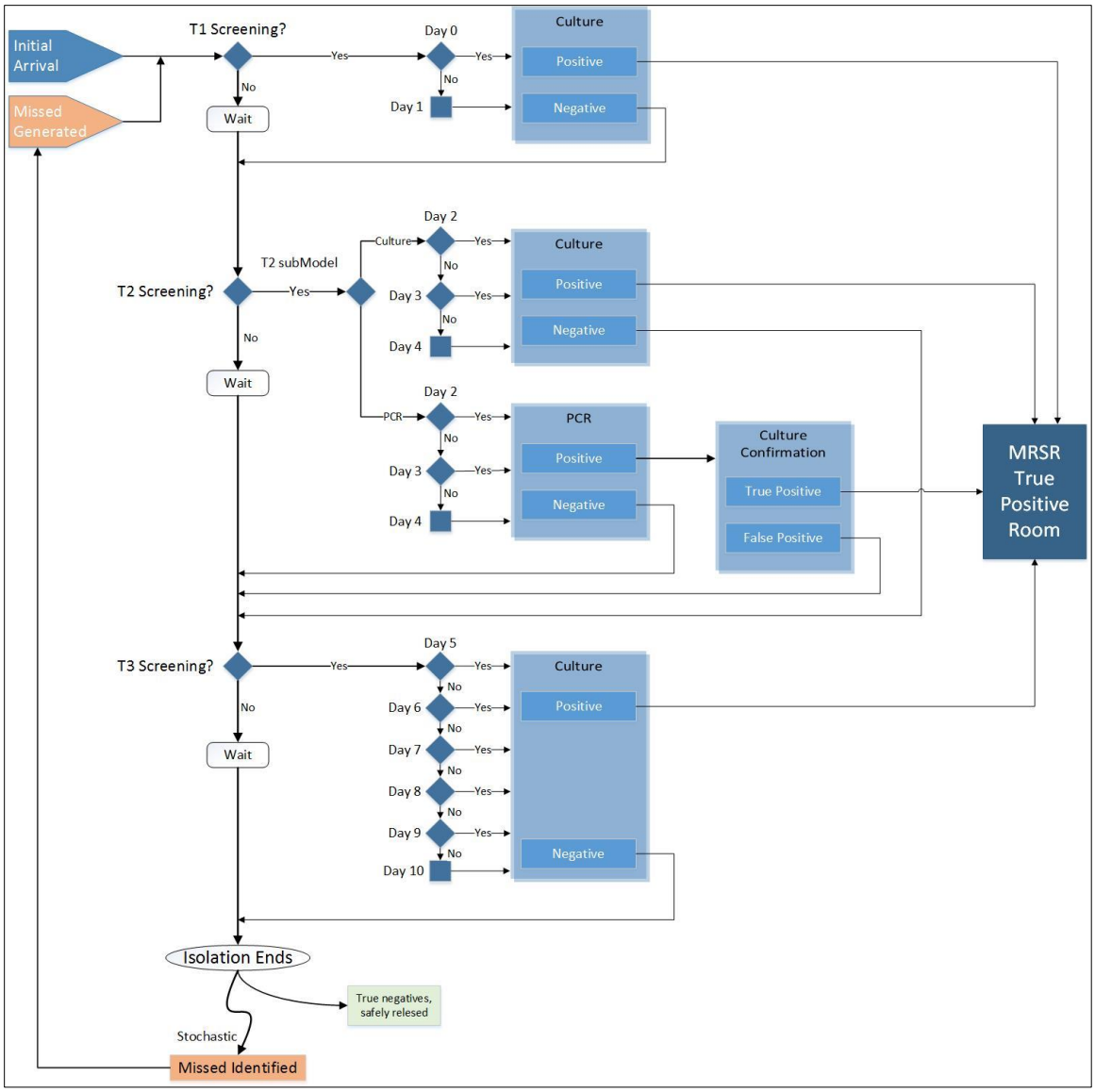

Figure 3.2: The conceptual model of the parameter estimation model

3.2.2 Model description and assumptions

When a new MRSA carrier is identified; all exposed roommates will be placed into isolation with follow-up screening. The number of the roommate(s) is 1 if the case is identified in a semi-private room (equipped with 2 beds) or 3 if the carrier is identified in a cohort room (equipped with 4 beds). However, if a carrier is defined in a cohort room and the patient had previously spent several days in a semi-private room. Then, the number of exposed roommates will be 4 in total. After roommates entered the system, some of them are screened at day 0 or day 1 with equal probability. If the result for an exposed roommate is positive, s/he is transferred to an MRSA-

positive room immediately. The negatives and the non-screened patients will remain in the isolation.

It is assumed that whether a patient has been previously screened or not would not affect the screening decision in the next time. T2 screening may be equally likely to be applied at day 2, 3, or 4 with culture or PCR tests exclusively.

Note that positive results from PCR need to be confirmed by a culture test. Similarly, the true positives will be sent to the positive room; the negative and the non-screened cases will remain in system. The same procedures are applied in T3 as well, while the screening times are evenly distributed from day 5 to 10. The screened patients will be released from isolation when the screening results are reported. The isolation duration is 10 days for T3 non-screened patients deterministically. When isolation ends, patients will be discharged from the hospital or continue staying in the hospital. True negatives are safely released from isolation; however, the false negatives will cause more contacts.

3.2.3 Transmission and progression sub-model

If an exposed patient develops MRSA colonization or infection during the isolation, s/he will not affect anybody else in a semi-private room; however, in cohort rooms, s/he may spread MRSA to the other non-colonized patients. The transmission probability is positively correlated with the number of MRSA cases in the same room. In addition, patients might progress infections if they are colonized. Figure 3.3 shows the transmission and progression process during isolation. A patient's MRSA status are defined as non-colonized, colonized, and infected. It is assumed that a non-colonized case might become colonized during each day of isolation; and a colonized case might become infected with progression probability; however, the transition from a non-colonized to an infection within a day is assumed to be unlikely.

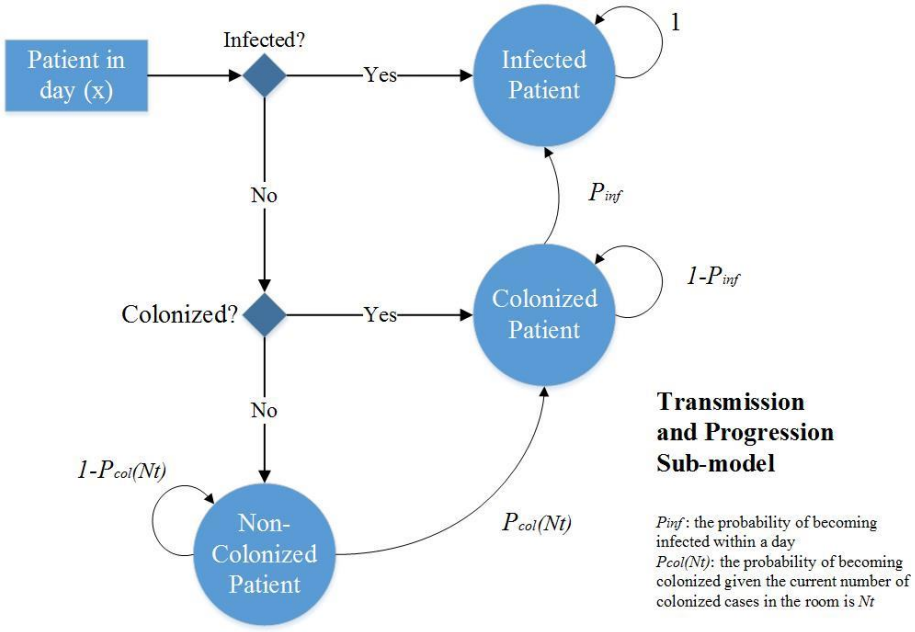

Figure 3.3: Transmission and progression sub-model

3.3 Data collection and processing

The input data is collected from peer reviewed articles and the retrospective data from Grand River Hospital and St. Mary's General Hospital (GRH&SMH). The data collection and processing are divided into the following four aspects - patient characteristics, screening procedures, transmission mechanisms, and the costs.

3.3.1 Patient characteristics

3.3.1.1 Arrivals

Simulation begins by generating the initial exposed roommates. Let T be the time between two contact breaks which is assumed to be completely random. The inter-arrival time is modeled as an exponential distribution with rate λ. The density function of T is:

$$f_T(t) = \begin{cases} \lambda e^{-\lambda t} & for\ \ t \geq 0 \\ 0 & for\ \ t < 0 \end{cases} \tag{3.1}$$

The mean of T:

$$ET = \int t f_T(t) dt = \int_0^{\infty} t \cdot \lambda e^{-\lambda t} dt = -te^{-\lambda t}|_0^{\infty} + \int_0^{\infty} \lambda e^{-\lambda t} dt = \frac{1}{\lambda} \tag{3.2}$$

Since the mean number of contact patients in a contact break, N_0, is estimated to be 3 (GRH & SMH) and the total number of exposed roommates N_{total} is 842 within 1706 days (Ng et al, 2012); then,

$$\frac{1706}{ET} \cdot N_0 = N_{total} \tag{3.3}$$

The mean of the time between arrivals is (days):

$$ET = 6.08; \tag{3.4}$$

And the arrival rate is estimated to be (λ patients / day):

$$\lambda = 0.165 \tag{3.5}$$

In addition, the arrival rate of the missed generated patients is modelled as a discrete probability distribution. Active screening is conducted weekly for the released roommates in GRH; the mean time of finding a missed case T_{miss} is suggested to be 7 days (GRH). The distribution of T_{miss} is assumed as,

$$\begin{cases} p(T_{miss} = 6) = 0.1 \\ p(T_{miss} = 7) = 0.8 \\ p(T_{miss} = 8) = 0.1 \end{cases} \tag{3.6}$$

3.3.1.2 The initial and the transmitted MRSA cases

As transmissions among roommates are likely, the total number of conversions N_{cvs} should include the initial MRSA cases (I_{mrsa}) and the newly transmitted MRSA cases (TR_{mrsa}). Initial cases are those who are colonized before isolation, while the transmitted are those who acquired MRSA during isolation. Therefore,

$$N_{cvs} = I_{mrsa} + TR_{mrsa} \tag{3.7}$$

3.3.2 Screening characteristics

Screening sensitivity, specificity and the turnaround time are the main characteristics of a screening method. The screening sensitivity of particular time period depends on the conversion rate within the time; however, they are not the same items. Table 3.2 shows the number of conversions detected from T1 to T3. Culture specificity is assumed to be 100% because in practice positives from culture tests are deemed as true positives. PCR specificity is calculated as

97.5% (Ng et al.). The mean turnaround time of culture is 24 hours and the time for PCR is 1 to 2 hours (GRH).

Table 3.2: Conversions detected in different time periods (Ng et al., 2012)

Time of post-exposure T(x)	Screening method	Roommates tested	Positives detected during follow-up screening	Positives detected at T(x) only	Conversion rate at T(x)	95% CI
T1	Culture	557	40	12	30%	(16-44)
T2 PCR	PCR	225	20	11	55%	(33-77)
T2	Culture	452	40	20	50%	(35-65)
T3	Culture	397	34	19	56%	(39-73)

3.3.2.1 Evaluating the minimum screening sensitivity

Conversion rates provide the lower bounds for the sensitivity values. Take T1 culture screened patients (N_1=557) for example, let D_1 be the number of already colonized patients among N_1 at T1; let F_1 be the number of newly transmitted cases among N_1 after T1; then, the total number of conversions from N_1 is the summation of D_1 and F_1. Therefore, the number of conversions detected from N_1 is,

$$(D_1 + F_1)R_{cul_{t1}} = D_1 S_{cul\_t1} \tag{3.8}$$

S_{cul_t1} denotes the culture sensitivity at T1; R_{cul_t1} is the proportion of conversions detected at T1. Since $F_1 \geq 0$, then,

$$S_{cul\_t1} \geq R_{cul\_t1} \tag{3.9}$$

Applying the same analyses for T2 and T3, similar results can be derived as following,

$$\begin{cases} S_{PCR\_t2} \geq R_{PCR\_t2} \\ S_{cul\_t3} \geq R_{cul\_t3} \end{cases} \tag{3.10}$$

and the lower bounds of sensitivities are:

$$\begin{cases} S_{cul\_t1(min)} = 30\% \\ S_{PCR\_t2(min)} = 55\% \\ S_{cul\_t3(min)} = 56\% \end{cases} \tag{3.11}$$

The minimum sensitivities are not the actual sensitivities; nevertheless, the estimation gives the initial input parameters for the simulation model and the minimum values will be increased during the model calibration.

3.3.2.2 Screening decisions from T1 to T3

Based on the assumption of independent screening selection, the proportion of exposed roommates screened in each time period of T1 to T3 can be derived from Figure 3.1 and Table 3.2. Let Ti denote the screening period and M_i be the correspondent screening method. Since 12 carriers were detected in T1, then

$$\begin{cases} p(T_i = T1, M_1 = \text{culture}) = \dfrac{557}{842} = 0.6615 \\ p(T_i = T1, M_1 = \text{no screening}) = 1 - 0.6615 = 0.3385 \\ p(T_i = T2, M_2 = \text{culture}) = \dfrac{452}{842 - 12} = 0.5446 \\ p(T_i = T2, M_2 = \text{PCR}) = \dfrac{225}{842 - 12} = 0.2711 \\ p(T_i = T2, M_2 = \text{no screening}) = 1 - 0.5446 - 0.2711 = 0.1843 \end{cases} \tag{3.12}$$

However, it is mentioned that all exposed roommates are screened at least once during the follow-up screening. Therefore, T3 screening must be enforced to those who had never been screened in T1 or T2. Let set $A = \{\text{Patients: } M_1 = M_2 = \text{no screening}\}$ denotes the patients who have not been screened before T3; then

$$p(T_i = T3, M_3 = \text{culture} | \text{Patient} \in A) = 1\ ; \tag{3.13}$$

The number of patients in system after T2 screening results reported is approximately to be 799 (842-12-11-20); the number of patients who have neither been screened in T1 nor in T2 is approximately to be 52 (153×285÷842); therefore, the screening probabilities for those who been screened in T1 or T2 are

$$\begin{cases} p(T_i = T3, M_3 = \text{culture} | \text{Patient} \notin A) = \dfrac{397 - 52}{799 - 52} = 0.4618; \\ p(T_i = T3, M_3 = \text{no screening} | \text{Patient} \notin A) = 1 - 0.4606 = 0.5372; \end{cases} \tag{3.14}$$

3.3.3 The transmission probabilities

3.3.3.1 Modeling the transmission mechanism as a Markov Chain

Transmission is the core element within the simulation which decides how aggressively MRSA spread from the unknown carrier to the non-colonized patients. The transmission mechanism is modeled as a Markov Chain in both semi-private rooms and cohort rooms. MRSA statuses are defined as non-colonized, colonized, colonize detected, and infection. Since no infection was

reported within the 842 patients, the infection probability is assumed to be 0. Therefore, the transmission mechanism will consider the transitions among the non-colonized, colonized, and colonized detected cases only.

Let X_n denote the number of patients in each MRSA status with the format of "$N_{nc}N_cN_{cd}$"; $N_{nc}, N_c, and\ N_{cd}$ are the numbers of non-colonized, colonized, colonized detected cases, respectively ($N_{nc} + N_c + N_{cd} \leq 4$ and $N_{nc}, N_c, N_{cd} = 0,1,2,3,4$). It is assumed that a patient's MRSA status only depends on the patient's MRSA status today; then, X_n is a discrete Markov Chain with the state space of

$$\left\{\begin{array}{c} 400, 310, 301, 220, 211, 220, 202, 130, 121, 112, 103, 040, 031, 022, 013, 004, \\ 300, 210, 201, 120, 111, 102, 030, 021, 012, 003, \\ 200, 110, 101, 020, 011, 002, \\ 100, 010, 001, \\ 000 \end{array}\right\}$$

and the transition matrix

$$P(i,j) = P(X_{n+1} = j | X_n = i) \tag{3.15}$$

where the transition probability does not depend on time n. And the probability is affected by the number of current colonized patients N_c in the room. Then, the transmission probability during isolation $p_{iso\_mrsa}(N_c)$ is

$$p_{iso\_mrsa}(N_c) = 1 - (1 - p_{iso})^{N_c} \tag{3.16}$$

During a non-screening day, the transition probabilities are

$$\begin{aligned} &\mathrm{P}(X_{n+1} = N_{nc-l}N_{c+l}N_{cd} | X_n = N_{nc}N_cN_{cd}) \\ &\qquad = \binom{N_{nc}}{l} (p_{iso\_mrsa}(N_c))^l \left(1 - p_{iso\_mrsa}(N_c)\right)^{N_{nc}-l}, \qquad (3.17) \\ &\qquad l = 0,1,2,3,4 \end{aligned}$$

$$\mathrm{P}(X_{n+1} = N_{nc-k}N_cN_{cd+k} | X_n = N_nN_cN_{cd}) = 0, \qquad k = 0,1,2,3,4 \tag{3.18}$$

$$\mathrm{P}(X_{n+1} = N_{nc}N_{c-m}N_{cd+m} | X_n = N_nN_cN_{cd}) = 0, \qquad m = 0,1,2,3,4 \tag{3.19}$$

$$\mathrm{P}(X_{n+1} = N_{nc+t}N_{c-t}N_{cd} | X_n = N_nN_cN_{cd}) = 0, \qquad t = 0,1,2,3,4 \tag{3.20}$$

Formula (3.17) shows the probability of having l patient(s) become contaminated when the current number of colonized patient(s) in the room is N_c. Formula (3.18) and (3.19) illustrate that no detection is possible without screening. The last equation shows that a patient will stay colonized when no decolonization is applied.

In comparison, the transition probabilities during a screening day are

$$\begin{aligned} \mathrm{P}(X_{n+1} = N_{nc-l}N_{c+l-k}N_{cd+k} | X_n = N_{nc}N_cN_{cd}) \\ = \binom{N_{nc}}{l} \binom{N_c}{k} \left(p_{iso\_mrsa}(N_c)\right)^l \Big(1 \\ - p_{iso\_mrsa}(N_c)\Big)^{N_{nc}-l} s^k (1-s)^{N_c-k}, \qquad l,k = 0,1,2,3,4 \end{aligned} \tag{3.21}$$

$$\mathrm{P}(X_{n+1} = N_{nc-m}N_cN_{cd+m} | X_n = N_{nc}N_cN_{cd}) = 0, \qquad m = 0,1,2,3,4 \tag{3.22}$$

$$\mathrm{P}(X_{n+1} = N_{nc+t}N_{c-t}N_{cd} | X_n = N_{nc}N_cN_{cd}) = 0, \qquad t = 0,1,2,3,4 \tag{3.23}$$

Formula (3.22) indicates the probability of having l more colonized patient(s) given the current number of MRSA cases is N_c. In addition, each colonized case will be identified with probability s assuming that a new transmitted case cannot be detected in the same day as he or she acquired MRSA. Equation (3.23) claims that a non-colonized cannot transit to a detected case since the specificity is assumed to be 100% (assuming that this is a culture test). The last equation shows that a colonized case cannot transit to a non-colonized without therapy.

Replacing the transmission probability of in-isolation, p_{iso_mrsa}, with the probability of not-in-isolation, p_{noniso_mrsa}, we use the same mechanism to calibrate the prevalence of MRSA among the roommates at the beginning of isolation at day 0.

3.3.3.2 The ratio of effectiveness

Transmission rates proposed in the literature for Canadian hospitals are presented in Table 3.3. Although these rates are not specified as the transmission probabilities among the exposed roommates directly; the data can be used for estimating the transmission probabilities among the roommates.

Table 3.3: Rate of transmission of MRSA per day (Tübbicke et al., 2012)

Study	Transmissions per day (in-isolation)	Transmissions per day (not-in-isolation)
Canada (2007)	0.0013	0.0041
Canada (1996)	not reported	0.048
Canada (2005)	0.00081	0.00137

Let P_{un_iso} be the transmission probability of not-in-isolation (per patient per day), and P_{iso} be the transmission probability of in-isolation. Then, P_{un_iso} indicates how aggressively a colonized patient spreads MRSA among the un-isolated patients, whereas P_{iso} illustrates how aggressively

MRSA spreads among the isolated ones. Therefore, the ratio (*e*) between the transmission probabilities of not-in-isolation and in-isolation can be deemed as an indication of how effective isolation is in preventing MRSA transmission. That is,

$$e = \frac{P_{un\_iso}}{P_{iso}} \tag{3.24}$$

When *e* is high, isolation is effective in preventing transmissions; on the contrary, when *e* is low (e.g. $e = 1$), isolation is deemed as ineffective since it does not reduce the transmission probability at all. Table 3.4 shows ratios in two Canadian hospitals described above.

Table 3.4: The ratio between the transmission probabilities

	R_{iso}	R_{un_iso}	e	Average
Canada 2007	0.0013	0.0041	3.154	2.423
Canada 2005	0.00081	0.00137	1.691	

We assumed that the specific transmission probabilities could be different from setting to setting; however, the effectiveness levels should be comparable with or not deviate too much from each other among the hospitals in the same state because of having the same population. Measuring the impact of implementing isolation under different effective levels can be achieved by changing the ratio *e*. Literature shows the average ratio is 2.423 (range: 1.691-3.154). In this study, isolation is assumed to be effectively applied in both North York General Hospital and Grand River Hospital. Therefore, 3.154 is selected as the base case ratio for calculating the transmission probability of in-isolation. Then,

$$\frac{P_{un\_iso}}{P_{iso}} = 3.154 \tag{3.25}$$

Note that the value of P_{un_iso} and P_{iso} will be adjusted during the model calibration by taking the *e* constant. That is, P_{un_iso} and P_{iso} will be calibrated by only changing one of them. In Section 3.5, the model will be calibrated according to different *e* values – the lowest (1.691), average (2.423), and highest (3.154). The highest ratio will be the base case.

3.3.4 Costs

Costs are classified into screening cost (culture and PCR), isolation cost, colonization management cost, and infection treatment cost. Multiple values have been reported in the literature; however, they may not be represented in the same currency unit or the same year value.

To make the costs comparable with each other, exchange rates from the correspondent years are applied to convert the costs into Canadian dollar (CAD). And then, the consumer price index (CPI) in health care is applied to convert all numbers into the value of 2010. Table 3.5 provides the exact values in literature and the converted values with exchange rates and CPI applied.

Table 3.5: Costs list

Exact cost values in the literature	Converted values with exchange rates and CPI applied (CAD, 2010)	Source
Screening Cost		
PCR test Cost		
41.32 (USD)	42.65	Nyman et al. (2011)
20.5 (EUR)	26.16	Tübbicke et al. (2013)
50.27 (USA)	51.37	Lee et al. (2011)
Culture test Cost		
18.27 (USD)	18.86	Nyman et al. (2011)
12.34 (USD)	12.61	Lee et al. (2011)
Isolation Cost		
62.77 (EUR)	80.08	Tübbicke et al. (2013)
134.96 (EUR)	183.26	Tübbicke et al. (2012)
95.59 (EUR)	156.06	Tübbicke et al. (2012)
MRSA Colonization Cost		
5,235.14 (CAD)	6,622.77	Giuseppe et al. (1999)
1,363 (CAD)	1,614.58	Kim et al. (2001)
MRSA Infection Cost		
14,360 (CAD)	17,010.58	Kim et al. (2001)
7,693 (CAD)	8,819.51	Rosner et al. (2004)
8,444 (CAD)	9,680.48	Rosner et al. (2004)
6,149.08 (EUR)	8,349.84	Tübbicke et al. (2012)

Based on the converted values from Table 3.5, the cost range can be derived by taking the minimum and the maximum cost as the lower bound and the upper bound respectively. The base case values are generated by taking the average costs under each cost item. The detailed ranges are provided in Table 3.6.

Table 3.6: Cost ranges

	Base case (average)	Lower bound	Upper bound
PCR Cost	40.06	26.16	51.37
Culture Cost	15.73	12.61	18.86
Isolation Cost	139.80	80.08	183.26
MRSA Colonization Cost	4,118.68	1,614.58	6,622.77
MRSA Infection Cost	10,965.10	8,349.84	17,010.58

3.4 Simulation modelling with Arena

Arena Standard and Professional Editions are offered by Rockwell Automation. Arena is a general-purpose simulation software that can be applied for simulating both discrete and continuous systems (Banks et al., 2009). Simulation provides a computerized model of a real or proposed system for the purpose of conducting experiments and helps to understand the system behaviors under different conditions (Kelton et al., 2010). Simulation can be utilized for predicting the effect of the new disruptive policies before they are implemented for trial. In this study, an Arena model is built based on the conceptual model described in Section 3.2. With the initial input parameters presented in Section 3.3, the Arena model will be calibrated in estimating the baseline values of the parameters. This section will introduce how modules within Arena templates are utilized in having the operational model.

3.4.1 Module description

Patients are created into the system from the Create Module at simulation time 0. They may be assigned with attributes such as MRSA colonized or non-colonized with a probability that is equal to the prevalence level. Roommates who are isolated in a semi-private room or cohort room is realized by assigning different attribute values for distinguishing in which room type they are isolated.

When patients enter the system, transmission and progression start. Based on their MRSA status, the Decide Module distinguishes the colonized patients from the non-colonized patients. The colonized patients may be assigned with MRSA infection, while the non-colonized patients may become colonized by assigning MRSA colonization with a transmission probability. The probability is adjusted according to the number of MRSA cases in the room at a specific day; a variable with a unique index (patient room) is introduced in storing the number of colonized cases.

Detecting the true positive cases is realized by assigning screening sensitivity to the colonized cases while the true negatives are achieved by assigning with the specificity. When all screening assignments made and the transmission and progression assignments done, patients will enter the Dispose Module and the isolation ends. Patients who were assigned with MRSA colonized but failed to be detected are deemed as the missed cases. When a missed case is released for a certain amount of time, a signal will be sent to the Hold (connected with another Create Module), and more patients will be created into the system.

3.4.2 Replication parameters

The replication parameters include the warm-up period, the length of replication, the number of replications, the initialization between replications, the time unit etc. Figure 3.4 shows the setup for these parameters. Specifically, the number of replications is 500 with each replication length equaling 1706 days. The length is calculated based on the starting and ending dates provided in the paper (Ng et al., 2012) with no warm-up period required. The stating date and time were specified to be June 2005 and the specific time is assumed to be 8:00 AM on June 15.

The initialization between replications is set as follows: 1) all statistics are cleared between simulation replications; 2) the system is re-initialized - all entities are removed from the system and the defined variables are restored to their default values. This initialization guarantees that each replication is identical and independent from the others.

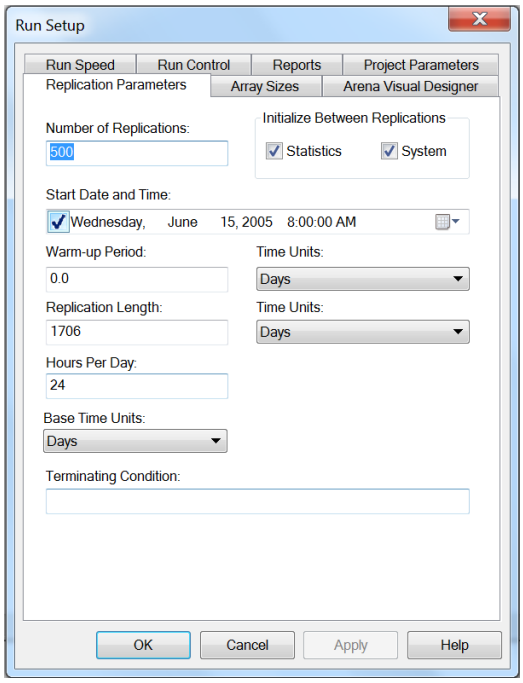

Figure 3.4: Setup for the replication parameters

3.5 Verification, calibration, and validation of the model

The validity of the simulation is achieved by verification and validation. Model verification has been done by comparing the computerized representation (operational model) with the conceptual model, which includes representing the system components and assumptions correctly, and

entering the data accurately. Figure 3.5 shows the general relationship between verification, validation, and calibration.

Naylar and Finger (1967) formulated a three-step validation process which is widely followed: build a model with high face validity; validate model assumptions, and compare the input-output transformation in the simulation model and the transformation in the real system (as cited in Banks et al., 2009).

3.5.1 Model verification

The model has been verified for assuring that there is no coding mistake in the computerized model. After completing each module of the simulation model, we checked whether the module works reasonably as it is and whether it complies well with the other modules. For example, Patient Arrival Module is controlled by counting the number of arrived patients in each patient category before disease progression starts. In parameter estimation model, the total number of arrivals is around 842; the initial arrivals + the arrivals caused by the missed cases. If the total number of arrivals is unreasonably high given the correct the inter-arrival times, then there must be something wrong with the missed cases. The model is checked by searching the source of the missed cases, those who are assigned with false negatives. Is the input sensitivity wrong? Are the blocks within the model mistakenly connected with the branch of the missed cases?

Interestingly, we observed unreasonable results even if the flow chart seems correct. For example, when a missed case is identified, a new cycle of contact isolation will start. The first model we developed simulated the process by generating the missed-case caused arrival via duplicating the missed case directly; that is, the attributes (screening results, MRSA status, the time spent in isolation, etc.) of the missed case were also inherited by the missed-case caused roommates. The duplication of the attributes caused problems to the model as their time in the system was wrong. Confronted with this, we deleted the direct connection from the missed module to the duplication module, but added a Signal and a Hold: whenever a missed case found, a signal will be sent to the Hold, and the Hold will release a brand-new case into the duplication unit; thereby, the problem caused by the mistakenly assigned attributes resolved.

We resolved such cases until we are confident that each module of the simulation model works in the correct manner both individually and collectively.

3.5.2 Face validity

To achieve the face validity is to check whether the model behaves in the expected way when one or more input parameters change (Banks et al. 2009). In the simulated system, it can be expected that increasing the transmission probability during isolation will increase the number of newly transmitted cases as well as the total colonized cases; decreasing the T3 screening sensitivity would lead to more missed cases; increasing the infection probability would generate more infections given the other input parameters are kept the same, etc. These expected results have been justified by conducting sensitivity analysis.

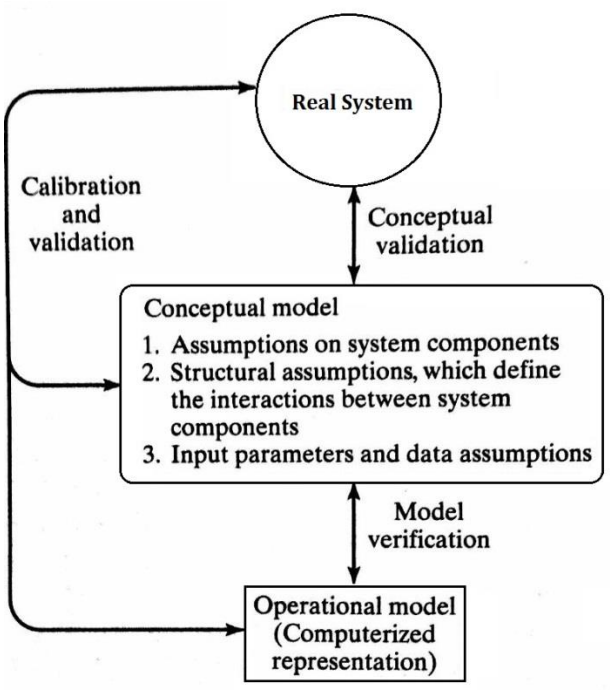

Figure 3.5: Model building, verification, and validation (Adopted from Banks et al., 2009)

3.5.3 Validate model assumptions (Conceptual validation)

We explained and discussed about our progress with Doctor William Ciccotelli. During the research meetings he went over the model assumptions, the conceptual model, and the data we used in the simulation modeling. For example, the initial version of the model was built base on the assumption that contact isolation rooms are limited number of resources: whenever a patient is defined as a contact, s/he will be moved to an available isolation room. However, Dr.Ciccotelli pointed that the roommates are isolated in the same room as they were in but only the initial identified carrier will be moved to another room. Additionally, the initial version did not

incorporate the T1 screening; therefore, the number of missed cases and the total colonized cases were found to be much higher than the numbers in real. After the model had been changed and adjusted for several iterations, he verified that the structure of system and the results of the simulation are reasonable.

3.5.4 Input-output validation and calibration

The input-output transformation and calibration are distinct concepts but usually achieved simultaneously (Banks et al., 2009). Using the historical data provided in the paper (Ng et al., 2012) as the benchmark statistics, the transformation validation can be processed by comparing the input-output from the operational model and the input-output in the hospital. However, entering the exact data collected from the hospital or the reasonably calculated numbers into the simulation model may not necessarily result in the same transformation even the model is verified based on the validated conceptual model; therefore, the model need to be calibrated. The iterative process of calibrating a model is presented in Figure 3.6.

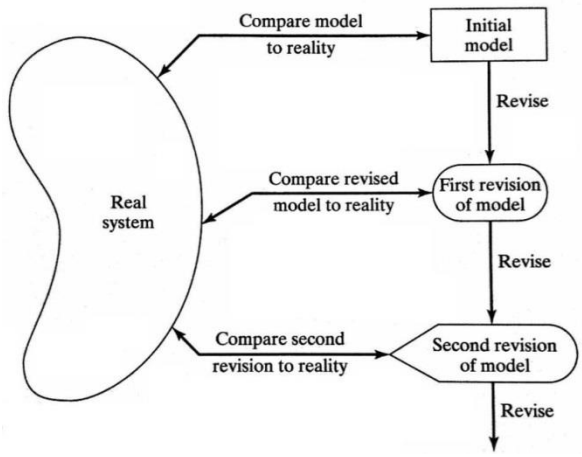

Figure 3.6: Iterative process of calibrating a model (Adopted from Banks et al., 2009)

During model calibration, parameters such as culture and PCR sensitivities and the transmission probabilities are adjusted iteratively for capturing the benchmark statistics. These values include the total conversion rate (8%), T1 conversion rate (30%, culture), T2 conversion rate (55%, PCR), and T3 conversion rate (56%, culture). The validated and calibrated results have been checked by Doctor William Ciccotelli, he confirmed that the model assumptions and the simulation outputs are reasonable. Table 3.7 and 3.8 provide the estimated parameters through calibration and the corresponding simulation results. Note that the ratio between the transmission probability of in-isolation and not-in-isolation is denoted as *e*.

Table 3.7: Estimated parameters under different *e* values

Ratio *e*	**1.69**	**2.42**	**3.15**
Transmission probability in-isolation	0.0149	0.0108	0.0084
Transmission probability not-in-isolation	0.0252	0.0617	0.0269
T1 culture sensitivity	0.330	0.318	0.317
T2 PCR sensitivity	58.0%	57.5%	57.0%
T3 culture sensitivity	56.5%	56.4%	56.2%

Table 3.8: Calibrated results under different *e* values

Ratio *e*	**1.69**		**2.42**		**3.15**	
	Mean	Half width	Mean	Half width	Mean	Half width
Total exposed roommates	842.66	< 2.02	842.19	< 2.09	840.71	< 2.03
Total conversions	67.33	< 0.82	67.34	< 0.82	66.99	< 0.81
Total Conversion rate (benchmark 1)	8%		8%		8%	
Total Conversion rate (95% CI)	7.98% (7.89%-8.07%)		7.98% (7.89%-8.07%)		7.96% (7.87%-8.04%)	
Total transmitted	7.14		5.48		4.22	
Total detected	45.32	< 0.59	45.44	< 0.61	45.49	< 0.60
Missed cases	21.72	< 0.43	21.63	< 0.44	21.26	< 0.43
T1 culture screening						
Total conversions	44.33	< 0.62	44.61	< 0.63	44.11	< 0.62
True positive	13.31	< 0.33	13.33	< 0.31	13.17	< 0.32
Conversion rate (benchmark 2)	30%		30%		30%	
Conversion rate (95% CI)	30.13% (29.48%-30.78%)		29.99% (29.40% - 30.57%)		29.92% (29.31% - 30.53%)	
T2 PCR screening						
False positive	5.49	< 0.21	5.08	< 0.20	5.08	< 0.20
Total conversions	14.51	< 0.34	14.63	< 0.34	14.49	< 0.34
True positive	7.93	< 0.24	8.06	< 0.25	8.02	< 0.25
Conversion rate (benchmark 3)	55%		55%		55%	
Conversion rate (95% CI)	54.88% (53.65% - 56.11%)		55.11% (53.95% - 56.27%)		55.44% (54.21% - 56.67%)	
T3 culture screening						
Total conversions	17.19	< 0.39	16.94	< 0.38	16.82	< 0.36
True positive	9.68	< 0.28	9.55	< 0.28	9.5	< 0.26
Conversion rate (benchmark 4)	56%		56%		56%	
Conversion rate (95% CI)	56.38% (55.35% - 57.41%)		56.30% (55.19% - 57.41%)		56.57% (55.48% - 57.67%)	

Chapter 4

Policy Evaluation Models

In Chapter 3, unknown parameters such as screening sensitivity and the transmission probabilities have been estimated using an iterative calibration approach. In this chapter, we will describe how these parameters are utilized to compare the following policies in GRH and SMH: Policy 1) 7-day isolation and conducting culture tests at (post-exposure) day 0 and day 6; Policy 2) 3-day isolation and conducting a culture test at day 0 and a PCR test at day 3; Policy 3) 7-day isolation and conducting culture tests at day 6 only; Policy 4) 3-day isolation and conducting a PCR test at day 3 only.

4.1 Policy description

Policy 1 is the existing screening and isolation strategy for the exposed roommates in GRH and SMH. Policy 2 is the proposed strategy which attempts to take the advantages of PCR test (higher sensitivity and shorter turnaround time) and thereby reducing the isolation duration. The procedures under Policy 1 and 2 are shown in Figure 4.1 and 4.2, respectively.

Under both Policy 1 and 2, all roommates are screened with culture test at post-exposure day 0. Whenever a patient is identified with positive result, he or she will be transferred to an MRSA positive room immediately. And the rest of the roommates will stay in isolation continuously and wait to be screened with culture test at day 6 (Policy 1) or PCR test at day 3 (Policy 2). When the second test results become available, the true positives will be moved to the positive room and the negatives will be released from isolation. However, patients with false negative results (missed cases) will cause more contact patients into the system. (Notice that patients with positive PCR result and negative culture confirmation will be isolated for four more days and have another culture test at day 6.)

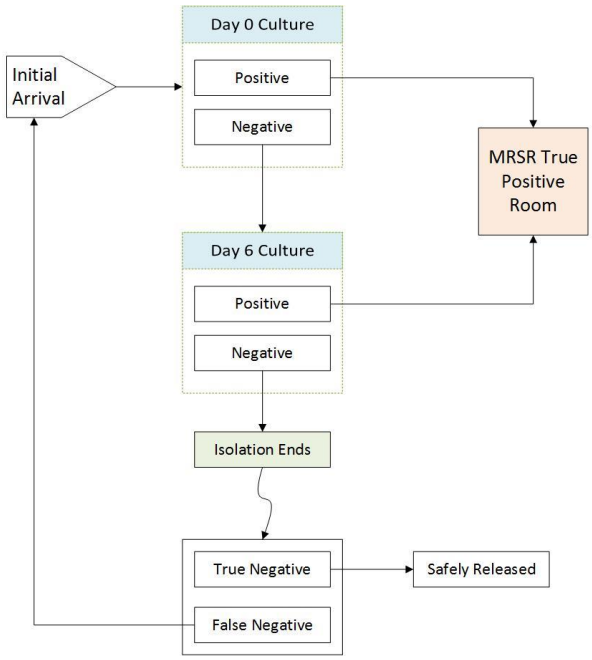

Figure 4.1: The screening and isolation procedure under Policy 1

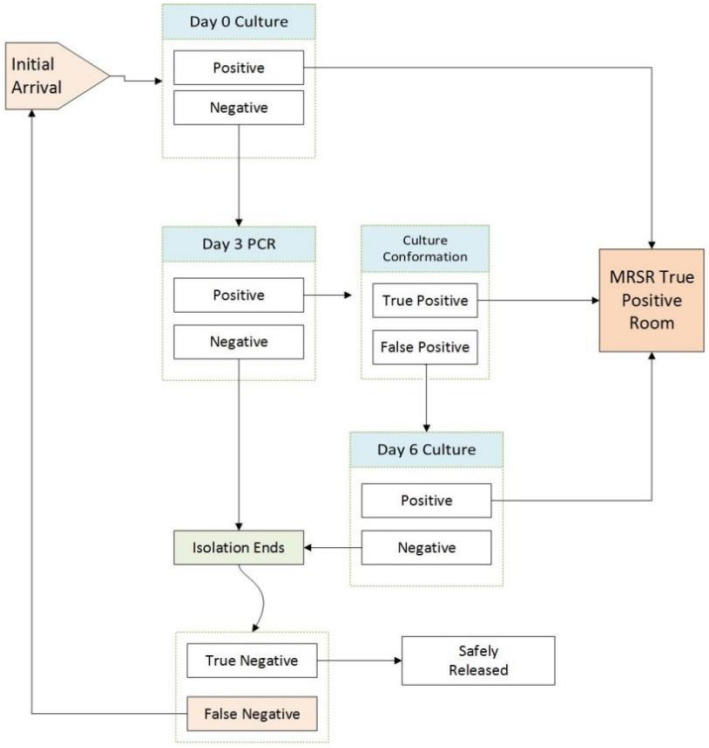

Figure 4.2: The screening and isolation procedure under Policy 2

Policy 3 and 4 are evaluated to examine the impact of day 0 screening. All procedures in Figure 4.1 and 4.2 remain the same but the element of day 0 culture screening is removed from Policy 1 and 2 for testing Policy 3 and 4, respectively.

4.2 Data assumptions

4.2.1 Sensitivity and transmission probabilities

Screening sensitivity is deemed as a property of a screening method; the sensitivities at T1 (day 0-1), T2 (day 2-4), and T3 (day 5-10) from North York General are directly applied to the day 0, 3, and 6 sensitivities in Grand River Hospital and St. Mary's General Hospital, respectively. In addition, the probability of MRSA spread from a colonized isolated patient or from a colonized un-isolated patient to a non-colonized case per day is assumed to be the same in the two hospitals.

4.2.2 Prevalence and room settings

The prevalence of MRSA among the exposed roommate is evaluated based on the transmission probability and the proportion of patients who have contact duration less than 48 hours' and who have more than 48 hours' contact durations. Additionally, the room settings are assumed to be the same in NYG and GRH with semi-private rooms equaling 20% and cohort rooms equaling 80% (GRH).

4.3 Operational model with Arena

4.3.1 Model transformation and utilization

The two policy evaluation models (model of Policy 1 and model of policy 2) are developed by extending the parameter estimation model in Chapter 3. The transformation is based on the conceptual model presented in Figure 4.1 and 4.2, respectively. For example, in the parameter estimation model, screenings are randomly conducted to the selected roommates at T1, T2, and T3. However, in the policy evaluation models, screenings are conducted among all roommates at day 0 and day 6 deterministically under Policy 1. Under Policy 2, T2 is performed at day 3. Table 4.1 illustrates the differences between the models that are discussed so far.

Table 4.1: Simulation model comparison

Model	Compared items	Parameter estimation model	Policy evaluation model	
			Model of Policy 1	Model of Policy 2
T1 Screening	Time	day 0 or 1	day 0	day 0
	Method	culture	culture	culture
	Screened roommates	selected	all	all
T2 Screening	Time	day 2, 3, or 4	-	day 3
	Method	culture or PCR*	-	PCR*
	Screened patients	selected	-	all
T3 Screening	Time	day 5,6,7,8,9, or 10	day 6	day 6
	Method	culture	culture	culture
	Screened patients	selected	all	False positive from T2

* Positives from PCR test will be confirmed with culture tests

To compare the performance of Policy 1 and 2, the parameter estimation model will be transformed according to the screening and isolation requirements of Policy 1 initially. And then the transformed model (model of Policy 1) will be modified slightly according to Policy 2 (model of Policy 2). Since the two policies are examined in the same hospital, the inter-arrival time, transmission probabilities, screening sensitivity at T1, etc. are assumed to be the same except for the isolation duration and the screening time(s) after day 0.

4.3.2 Replication parameters

The replication parameters are similar to the contents described in Chapter 3. The replication parameters include the number of replications, length of a replication, etc. The number of replications is 1000 with each replication length equaling 365 days. Since the length of each replication in the policy evaluation model is only one year instead of 5 years in the estimation model, the number of replications can be increased to reduce the sample deviation without causing too much running time. At the beginning of each replication, the system is reinitialized and the variables are restored to their default values. Therefore, the 1000 replications will be able to generate 1000 sets of output data which are independent from each other. Figure 4.3 shows the parameters' setup within Arena (Replication parameters are the same for both model of Policy 1 and policy 2).

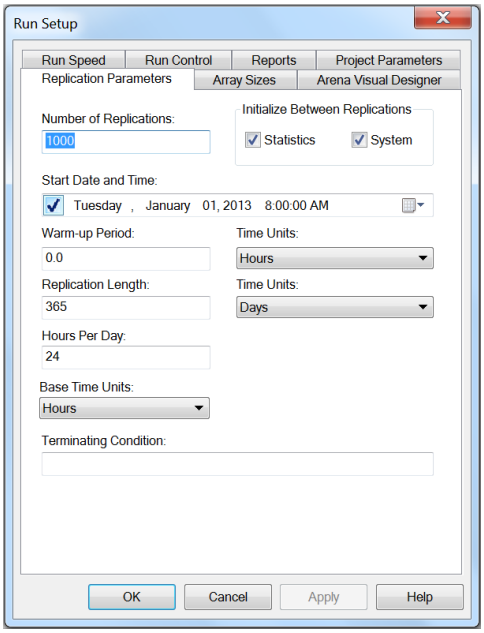

Figure 4.3: Replication parameters of the policy evaluation

4.3.3 Performance measures

The main outcomes of Policy 1 and Policy 2 are evaluated based on the number of colonized cases, missed cases, and newly transmitted cases, as well as the total costs involved in managing the exposed roommates within a year.

4.3.4 Model verification and validation

The model verification and validation are conducted based on the suggestions from Dr. William Ciccotelli and the historical data from GRH&SMH. Although no operating data can be collected directly from GRH or SMH for the model of Policy 2, validating the model of the proposed policy can be achieved by validating the model of the existed policy (Policy 1). Banks et al. (2009) validation increases the confidence that the model of the existing system is accurate; if the proposed system is a minor modification (might be a major change of the actual system) of the existed one, this confidence could be transferred from the existed to the proposed. Essentially, the differences between the simulation model of Policy 1 and 2 are minor since the modification only includes the numerical parameters' change (the number of isolation days and the screening sensitivity) but the logical structures of the two systems are almost the same. Dr. William confirmed the structure of the model is logical and the outputs from the model of the existing system are reasonable and very close to the data in 2013.

Chapter 5

Robustness Analysis

In Chapter 3 and 4, MRSA statuses are generally categorized as the non-colonized, colonized and infected. The colonized patients will be detected with the same probability at a particular day regardless of their different levels of colonization; the screening sensitivities are adjusted according to the sampling times only.

In this chapter, the screening sensitivity is assumed to be constant which is not affected by the sampling time. However, a false negative result is assumed to be caused by the patient's density of colonization. When the density reaches the detectable level, this carrier may be detected with a certain probability which equals the constant screening sensitivity; in contrast, when the density is lower than the detectable level, the case will become completely unobservable. Therefore, the colonized cases are further categorized as colonized-detectable and colonized-undetectable carriers. In Chapter 5, the transition probability from an undetectable status to a detectable status is estimated and then applied in model comparison.

5.1 Modeling the detectability of the disease

The transition from undetectable to detectable is modeled as a Markov Chain. It is assumed that whether an undetectable case will become detectable tomorrow only depends on the patient's detectability today. A simulation approach is applied in finding the stationary probability of the transition. The transitions between the states are shown in Figure 5.1.

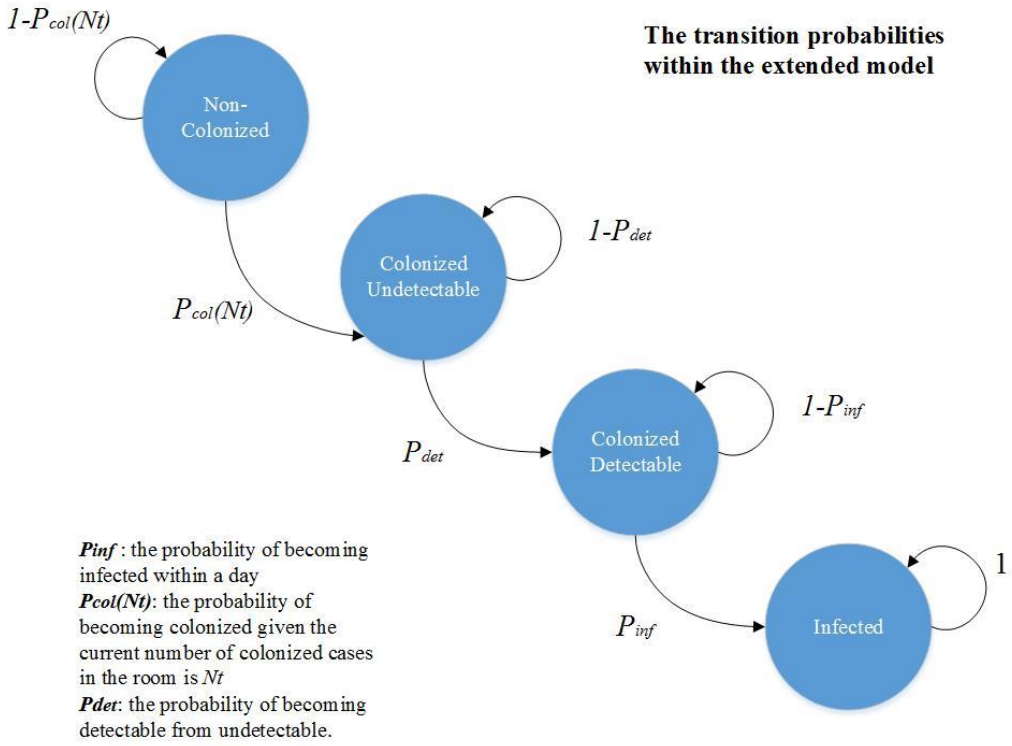

Figure 5.1: The transition probabilities within the extended model

5.2 Calibrating the probability of becoming detectable

The proportion of detectable cases at isolation day 0 is adjusted according to the conversion rate at T1 (30% by culture tests); this proportion provides the initial distribution of the detectable and the undetectable cases among the already colonized cases at the beginning of isolation. In order to find the probability of becoming detectable for an undetectable case per day, P_{det}, the parameter-estimation model in Chapter 3 is re-utilized in calibrating the probability. However, the original transmission process among the MRSA states (Figure 3.3) is replaced with the one shown in Figure 5.1. Specifically, the transmission probabilities except P_{det} are assumed to be the same as the previously estimated values under the base case and constant screening sensitivities (80.6% for PCR and 69.4% for culture) instead of the time-varying screening sensitivities estimated in Section 3. These constant screening sensitivities are estimated using the confirmation screening results of cases with known MRSA colonization from Grand River Hospital and St. Mary's hospitals in Kitchener ON. Therefore, the only unknown parameter is P_{det}, and the conversion rates at different times can be incorporated by changing P_{det} only. The benchmark statistics (Ng et al. 2012) for calibrating the probability include the conversion rate in T1 (30%, culture), T2

(55%, PCR; 50%, culture), T3 (56%, culture), and the total conversion rate (8%). The main input parameters and the calibration results are presented in Table 5.1 and Table 5.2, respectively.

Table 5.1: Main input parameters within robustness analysis

Transmission probability in-isolation	0.0084
Transmission probability not-in-isolation	0.0269
Culture sensitivity	0.317
PCR sensitivity	69.4%
T3 culture sensitivity	80.6%

Table 5.2: Calibration results under several P_{det} values

P_{det}	**0.240**	**0.253**	**0.260**
Total exposed roommates	843.80	841.61	843.34
Total conversions	67.09	67.33	67.57
Conversion rate (benchmark; simulation)	8%; 7.95%	8%; 8.00%	8%; 8.01%
T1 culture screening			
Total conversions	44.45	44.86	44.79
True positive	13.31	13.63	13.53
Conversion rate (benchmark; simulation)	30%; 29.94%	30%; 30.40%	30%; 30.20%
T2 culture screening			
Total conversions	29.22	29.23	29.58
True positive	13.54	13.91	14.13
Conversion rate (benchmark; simulation)	50%; 46.33%	50%; 47.60%	50%; 47.76%
T2 PCR screening			
Total conversions	14.49	14.48	14.62
True positive	7.74	8.02	8.06
Conversion rate (benchmark; simulation)	55%; 53.44%	55%; 55.39%	55%; 55.13%
T3 culture screening			
Total conversions	17.36	17.05	16.88
True positive	10.01	9.99	9.95
Conversion rate (benchmark; simulation)	56%; 57.68%	56%; 58.59%	56%; 58.96%
Root-mean-square error	0.0433	*0.0348	0.0372

* Minimum root-mean-square error

5.3 Applying P_{det} for policy comparison

After P_{det} is estimated from model calibration (0.253, which minimizes the root-mean-square error between the simulated conversion rates and the benchmark statistics), the policies are compared by using the progression probability of P_{det} and the constant screening sensitivities (80.6% for PCR and 69.4% for culture). In this case, the transmission and progression process within the policy-evaluation models (Chapter 4) is substituted with the one shown in Figure 5.1 as

well. Fortunately, this assumption allows comparing the performances of screening at day 1, 2, 3, 4, etc. instead of comparing the effect of screening at day 3 with PCR and day 6 with culture only. Specifically, the following policies will be evaluated with the policy-evaluation model in Chapter 4, respectively:

7-day isolation and conducting culture tests at (post-exposure) day 0 and day 6;
1-day isolation and conducting a culture test at day 0 and a PCR test at day 1;
2-day isolation and conducting a culture test at day 0 and a PCR test at day 2;
3-day isolation and conducting a culture test at day 0 and a PCR test at day 3;
4-day isolation and conducting a culture test at day 0 and a PCR test at day 4;
5-day isolation and conducting a culture test at day 0 and a PCR test at day 5;
6-day isolation and conducting a culture test at day 0 and a PCR test at day 6;

Decisions will be made based on the number of colonized cases generated and the total cost involved in MRSA management within a year.

Chapter 6

Results

The comparison between the two policies is realized by running each simulation model in Chapter 4 for 1000 times with each run consisting of around 300 exposed room-mates within 365 days. The base case input parameters for the model of Policy 1 and Policy 2 are shown in Table 6.1. The base costs are calculated based on the literature and the data presented in Chapter 3. Parameters with regard to the prevalence, transmission probabilities, sensitivity, and specificity are estimated from the model calibration in Chapter 3. In addition, the time between arrivals is incorporated in the policy evaluation model itself when the total number of contact patients is targeted on 300.

Table 6.1: Summarized input parameters under the base case

Input parameters	Model of Policy 1	Model of policy 2
Culture cost	$15.73	$15.73
False positive confirmation cost	-	$15.73
PCR cost	-	$40.06
Isolation cost	$139.8	$139.8
Colonization cost	$4,118.7	$4,118.7
Time between arrivals (days)	3.92	3.92
Prevalence	7.5%	7.5%
Transmission probability	0.0084*	0.0084
Culture sensitivity day 0	31.7%	31.7%
Culture specificity	100%	100%
Culture sensitivity day 6	56.2%	-
PCR sensitivity day 3	-	57.0%
PCR specificity	-	97.5%

*0.0084 is the calibrated probability when the highest ratio of effectiveness *e* (3.15) is selected as baseline value.

6.1 An overview of the base case results

The correspondent simulation outputs are presented in Table 6.2. Results show that the number of colonized cases, missed cases, and the total transmitted cases from Policy 2 are consistently lower than those from Policy 1, and the total cost involved under the proposed policy is dramatically less than the expense in the existing system.

Table 6.2: Simulation output (categorized overview)

	Model of Policy 1		Model of Policy 2	
Performance measures	Average	Half width	Average	Half width
Total contact patients	301.91	< 2.08	300.61	< 2.07
Total MRSA cases	23.93		23.20	
Colonized cases before isolation	22.39	< 0.34	22.51	< 0.34
Transmitted cases during isolation	1.54		0.70	
Transmitted (day 0-1)	0.27	< 0.03	0.27	< 0.03
Transmitted (day 1-6 or day 1-3)	1.13	< 0.07	0.43	< 0.04
Transmitted (day 6-7)	0.13	< 0.02	-	-
Total true positive cases	16.32	< 0.27	16.18	< 0.26
Detected by/at day 0 screening	7.19	< 0.17	7.12	< 0.17
Detected by/at day 6(3) screening	9.14	< 0.20	9.08	< 0.20
False Positive cases	-	-	6.75	< 0.17
Total missed cases	7.30	< 0.19	6.91	< 0.18
Total cost	$394,663.88		$246,408.48	
Total screening cost	$9,307.72		$16,635.15	
Total isolation cost	$288,052.34		$134,697.72	
Total colonization cost	$97,303.82		$95,075.61	

The average number of colonized cases under Policy 1 is 23.93 within a year while the figure from Policy 2 is 23.20. The difference between the two numbers is 0.73, which accounts for 3.2% of the colonized cases under Policy 1. The average numbers of missed cases from Policy 1 and 2 are 7.30 and 6.91, respectively; the missed cases are expected to be reduced by 5.34% when the proposed policy is applied. Although the reductions in the number of colonized and missed cases are relatively small, Policy 2 is particularly effective in reducing the number of transmitted cases during isolation and saving the total expense in managing the exposed roommates.

Results show that the number of newly transmitted cases is 0.70 from Policy 2 and 1.54 from Policy 1; the total cost involved in screening, isolation, and managing the colonized cases will be $394,664 for Policy 1 and $246,408 for Policy 2, respectively. Thus, the proposed policy is projected to reduce the total transmitted cases by more than 50% and save the total expense by $148,256, which is around 37.5% of the current expenses. Although an extra of $7,327 (16,635 - 9,307) will be spent in screening under the proposed system; the cost saved from isolation ($153,355) is more than enough for compensating the extra cost from the screening.

6.2 Statistical analysis

The differences between the two policies on the number of colonized cases, missed cases, and the new transmitted cases are assessed by paired-t-Test. Since 1000 sets of data are generated from

the 1000 replications, and each set of data includes a specific number of colonized, missed, and transmitted cases, etc. Thus, statistical analysis can be conducted based on the collected samples shown below (Table 6.3).

Table 6.3: Simulation results by replications

	Colonized cases			**Missed cases**			**Transmitted cases**		
Replication	Policy1	Policy2	Difference	Policy1	Policy2	Difference	Policy1	Policy2	Difference
1	28	22	6	7	4	3	4	0	4
2	20	23	-3	8	7	1	1	0	1
3	33	27	6	14	15	-1	1	1	0
4	26	28	-2	11	12	-1	0	5	-5
5	31	26	5	11	8	3	4	0	4
6	25	25	0	6	8	-2	3	0	3
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.	.	.
997	25	25	0	6	8	-2	1	1	0
998	34	14	11	13	1	12	3	0	3
999	25	31	-6	10	13	-3	0	1	-1
1000	25	27	-2	8	10	-2	3	1	2

The paired t-test results on the sample of the colonized, missed, and the transmitted cases are presented in Table 6.4. For example, the hypothesized difference between the means of colonized cases from Policy 1 and 2 is 0 while the two-tailed P-Value is 0.0026; under the significance level of 0.01, the null hypothesis that the difference between the means equals 0 is rejected. It is concluded that the number of colonized cases from Policy 2 is less than that from Policy 1. The 95% confidence interval for the difference (in the number of colonized cases) is calculated using the following equations:

$$\bar{X} = 0.724 \tag{6.1}$$

$$t = \frac{\bar{X} - X_0}{S_X/\sqrt{n}} = \frac{0.724 - 0}{7.5727/\sqrt{1000}} = 3.0234 \tag{6.2}$$

$$-t_{0.025(999)} < t < t_{0.025(999)} \tag{6.3}$$

$$95\%\ CI\text{: } \bar{X} - t_{\alpha/2}\frac{S_X}{\sqrt{n}} < D_0 < \bar{X} + t_{\alpha/2}\frac{S_X}{\sqrt{n}} \tag{6.4}$$

Table 6.4: The paired t-Test results on the performance measures

		Policy 1	Policy 2	Difference (X)
Colonized cases	Mean	23.928	23.204	0.724
	Standard deviation	5.6045	5.6487	7.5727
	Half width (95% CI)	0.3478	0.3505	0.4699
	P-Value (two-tail)	-	-	0.0026
Missed cases	Mean	7.301	6.908	0.393
	Standard deviation	3.1417	2.9158	4.1993
	Half width (95% CI)	0.195	0.1809	0.2606
	P-Value (two-tail)	-	-	0.0032
Transmitted cases	Mean	1.536	0.691	0.845
	Standard deviation	1.3025	0.8463	1.5683
	Half width (95% CI)	0.0808	0.0525	0.0973
	P-Value (two-tail)	-	-	2.41E-57

Statistical significance tests are applied to the number of missed and the transmitted cases by using the data in Table 6.3 and procedures in the Section 6.2. The summarized information on the paired t-Test is presented in Table 6.4. The hypothesis test indicates that the difference between the mean number of missed (or transmitted) cases associated with Policy 1 and Policy 2 is significant ($P < 0.01$).

6.3 One-way sensitivity analysis

It is important to remind that the data available on MRSA progression among the exposed room-mates is limited and Ng et al. (2012)'s study is the one with the largest sample size with regard to PCR testing among the exposed roommates in Canadian settings. That is why we derive most of the sensitivities and disease transmission probabilities based on the data provided by a single study. Although the outcomes of the proposed model is close to the statistics from GRH&SMH (e.g., 7.9% vs 6.5% MRSA colonization, respectively), some of the derived input parameters may be associated with variability due to limited existing data to estimate them, assumptions we made, or the variability in the timing of the considered screenings. Therefore, it is paramount to conduct sensitivity analyses to examine the effect of variance in such parameters on performance measures such as the total cost, the number of colonized, missed cases, and the newly transmitted cases. First, one-way sensitivity analysis (i.e. changing one parameter at a time and holding all the other parameters as constants) is conducted on the proposed simulation model under the base case.

Table 6.5: Range of the input parameters

Input Parameter	Base Case	Lower Bound	Upper Bound
PCR cost	$40.06	$26.16	$51.37
Culture cost	$15.73	$12.61	$18.86
False positive confirmation cost	$15.73	$12.61	$18.86
Isolation cost	$139.80	$80.08	$183.26
MRSA colonization cost	$4,118.68	$1,614.58	$6,622.77
Transmission probability	0.0084	0	0.048
Prevalence	7.5%	4.4%	12.6%
Culture sensitivity (day 0)	31.7%	27.9%	35.5%
PCR sensitivity (day 3)	57.0%	52.0%	62.0%
Culture sensitivity (day 6)	56.2%	49.5%	62.9%

Table 6.5 shows the ranges of the input parameters for conducting the sensitivity analysis. The costs are adopted from Table 3.5. The upper bound and the lower bound of the transmission probabilities are taken from Tübbicke et al. (2012). The prevalence is collected by searching papers that report the prevalence among the exposed roommates only: the lower bound of the prevalence is found to be 4.4% (Evison and Muhlemann, 2008) and the upper bound is found to be 12.6% (Moore et al., 2008). Finally, the range of the screening sensitivity is calculated by taking the proportion of variance in the literature. According to Tübbicke et al. (2012), the mean of culture sensitivity is 92.4% among the general patient group (range: 78.1% - 100%); thus, the length of the interval is 21.9% (100% - 78.1%) which constitutes 23.7% (21.9% ÷ 92.4%) of the mean with a half-width variation of 11.85% (23.7% ÷ 2). We assume that the variation of the screening sensitivity in our study is comparable to the variation in the literature. Then, the range of the culture sensitivity at day 6 is calculated as $56.2\% \pm 11.85\% \times 56.2\%$, which is (49.5% - 62.9%). Similarly, the range of the culture sensitivity (day 0) and PCR sensitivity (day 3) are calculatedly by using the data provided from Tübbicke et al. (2012).

6.3.1 Total cost

The baseline cost of Policy 1 is $394,664 and the cost of Policy 2 is $246,408. When the isolation cost is reduced to its lower bound ($80.80), the total cost involved in the whole procedure will decrease to $273,097 and $189,717 for Policy 1 and 2, respectively. On the contrary, if the isolation cost is increased to its upper bound ($183.26) and other parameters are held constant; then, the total cost will become to $484,212 and $288,282 for Policy 1 and 2, accordingly. The same procedure is repeated for all other parameters and the full outcomes are presented as follows:

Table 6.6: One-way sensitivity analysis on the total cost

Input parameter	**Policy 1** (baseline = $394,664)		**Policy 2** (baseline = $246,408)	
	Lower bound	Upper bound	Lower bound	Upper bound
Screening cost	$392,818	$396,516	$247,400	$255,123
Isolation cost	$273,097	$484,212	$189,717	$288,282
Colonization cost	$335,505	$453,823	$188,603	$304,212
Prevalence	$346,152	$478,526	$201,777	$322,021
Transmission probability	$382,153	$433,337	$237,047	$264,743
Sensitivity (day 0)	$397,638	$391,933	$247,417	$245,661
Sensitivity (day 6 or 3)	$399,059	$389,858	$247,655	$244,555

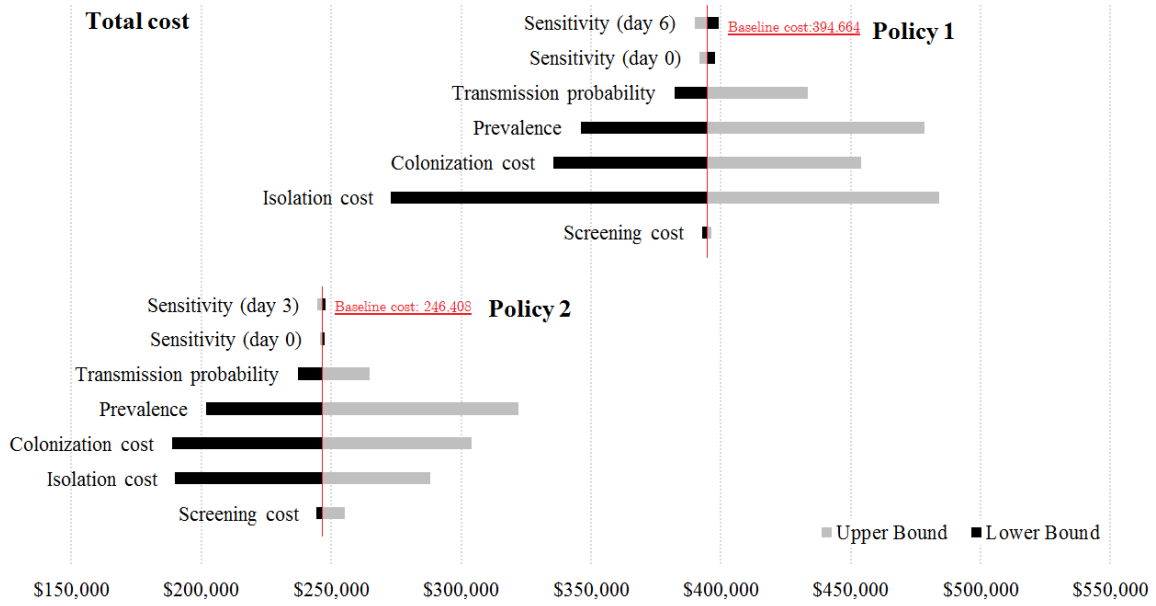

Figure 6.1: Cost comparison and sensitivity analysis on Policy 1 and Policy 2

Based on the recorded simulation results in Table 6.6, the total costs are plotted in Figure 6.1. It is clear that Policy 1 is associated with higher variance compared to Policy 2 when one of the model parameters is varied; thus, Policy 1 is affected from variability in the input parameters more than Policy 2. The total cost from Policy 2 is consistently lower than that from Policy 1 when the parameters are decreased to their lowest or increased to their highest.

The sensitivity analysis indicates that the isolation cost, the prevalence, and the colonization cost contribute to the most variability of the total cost. Comparing with policy 2, Policy 1 is more sensitive to the transmission probability during isolation but less sensitive to the screening cost. Although the screening procedure is applied to all patients, the variation of the screening cost

does not significantly affect the total cost. Screening sensitivity can also affect the total cost to a limited degree; results have shown that the increased sensitivity will lead to a lower total cost and the decreased sensitivity will lead to higher total cost.

6.3.2 Number of colonized cases

The one-way sensitivity analysis is repeated for the number of colonized cases with results presented in Table 6.7. The corresponding analysis and comparison is plotted in Figure 6.2.

Table 6.7: One-way sensitivity analysis on the number of colonized cases

	Policy 1 (Base case = 23.93)		Policy 2 (Base case = 23.20)	
Input parameter	Lower bound	Upper bound	Lower bound	Upper bound
Prevalence	13.769	41.960	13.234	40.248
Transmission probability	22.212	31.490	22.181	26.951
Sensitivity (day 0)	24.113	23.761	23.233	23.145
Sensitivity (day 3 or 6)	24.150	23.610	23.318	22.950

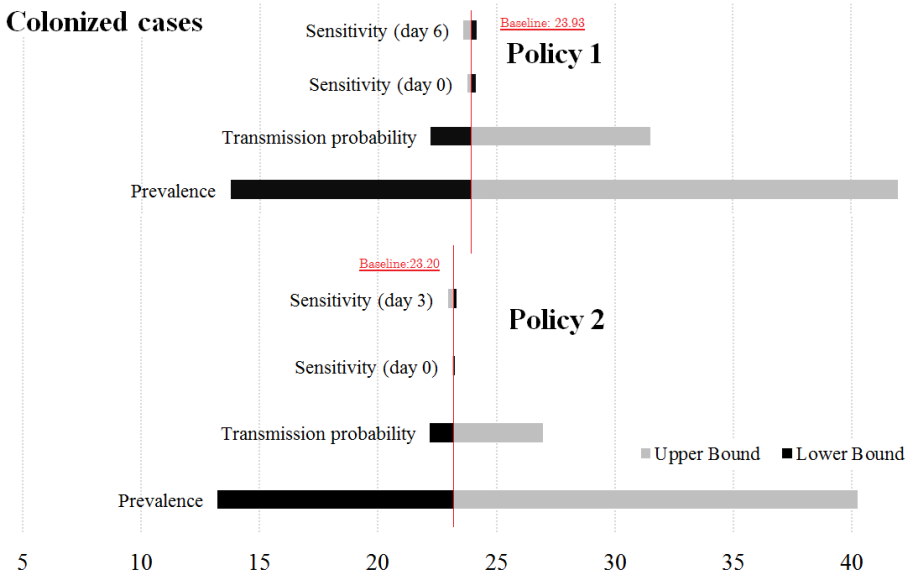

Figure 6.2: One-way sensitivity analysis and results comparison on the colonized cases

Table 6.7 shows that the number of colonized cases from Policy 1 and 2 under the baseline are 23.93 and 23.20, respectively. The number of the colonized cases from Policy 2 is consistently lower than that of Policy 1. When the transmission probability is 0, the difference between the number of colonized cases from Policy 1 and 2 is subtle.

Figure 6.2 shows that the number of colonized cases is most sensitive to the prevalence for both of the two policies: when the prevalence reaches at its upper (lower) bound, the number of the

colonized cases will increase (decrease) dramatically. The transmission probability contributes to the second highest variability of the colonized cases; when the probability is assumed to be as high as 0.048 per patient-day, the number of the colonized from Policy 2 will be lower than that from Policy 1, with 26.95 and 31.49, respectively. However, when the probability is assumed to be as low as 0, Policy 1 is expected to produce a little more colonized cases, with 22.21 for Policy 1 and 22.18 for Policy 2. In addition, the effect of the screening sensitivities for both Policy 1 and 2 are subtle.

6.3.3 Number of missed cases

As it is shown in Table 6.8, the baseline number of missed cases from Policy 1 and 2 are 7.30 and 6.91, respectively. Similar to the number of the colonized cases, the number of the missed cases is highly affected by the prevalence and the transmission probability: increasing either one of the parameters will significantly increase the missed number. However, decreasing the transmission probability cannot reduce the number of the missed or colonized by much (this is possibly due to the transmission probability under the base case is relatively low). Different than the number of colonized cases, the number of missed cases is sensitive to the screening sensitivity at day 6 (Policy 1) and day 3 (Policy 2). Still, the number of the missed cases is continuously lower in policy 2. When the transmission probability equals 0, the difference between the numbers of missed cases from the two policies is subtle.

Table 6.8: One-way sensitivity analysis on the number of missed cases

	Policy 1 (Baseline = 7.30)		**Policy 2 (Baseline = 6.91)**	
Input parameter	Lower bound	Upper bound	Lower bound	Upper bound
Prevalence	4.349	12.737	3.925	11.931
Transmission probability	6.505	10.690	6.495	8.450
Sensitivity (day 0)	7.818	6.836	7.258	6.509
Sensitivity (day 3 or 6)	8.442	6.159	7.694	6.023

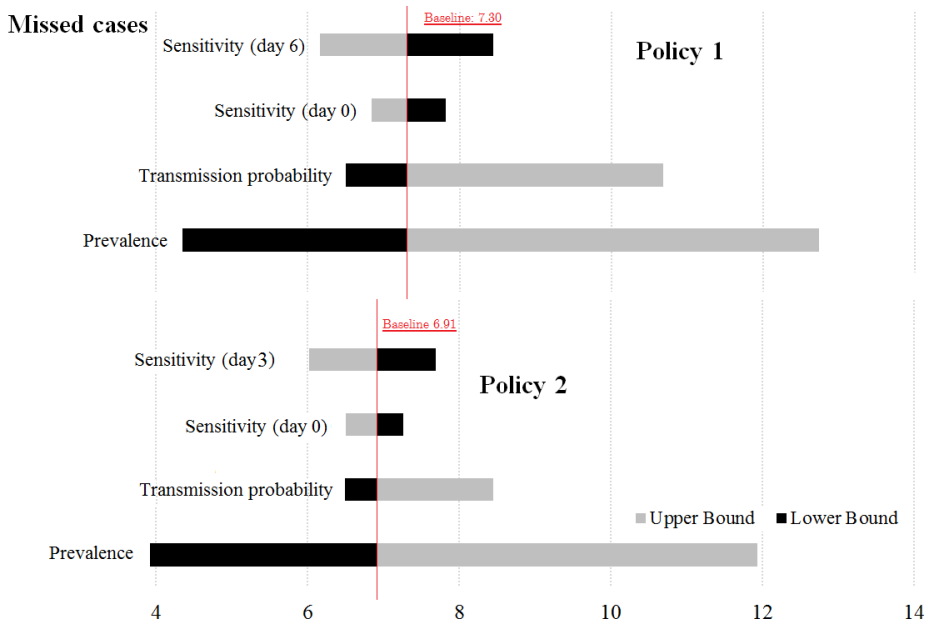

Figure 6.3: One-way sensitivity analysis and results comparison on the missed cases

6.3.4 Number of transmitted cases

Table 6.9 and Figure 6.4 indicate that Policy 2 is a dominant strategy in terms of saving the number of the transmitted cases during isolation. The number of the transmitted cases is dominantly affected by the transmission probability: higher probability is related with higher number of newly transmitted cases. The number of the transmitted cases from Policy 1 and 2 are 1.54 and 0.70 under the baseline; the increased probability and the prevalence will result in higher number of transmitted cases. However, Policy 2 has significantly lower number of transmitted cases than Policy 1 under all circumstances, the difference between the screening sensitivity of culture and PCR is not an identifiable factor of changing the number of the transmitted cases.

Table 6.9: One-way sensitivity analysis on the number of transmitted cases

	Policy 1 (Base case = 1.54)		**Policy 2 (Base case = 0.70)**	
Input parameter	Lower bound	Upper bound	Lower bound	Upper bound
Prevalence	0.888	2.429	0.413	1.224
Transmission probability	0.000	8.442	0.000	4.170
Sensitivity (day 0)	1.580	1.435	0.716	0.680
Sensitivity (day 3 or 6)	1.522	1.480	0.684	0.677

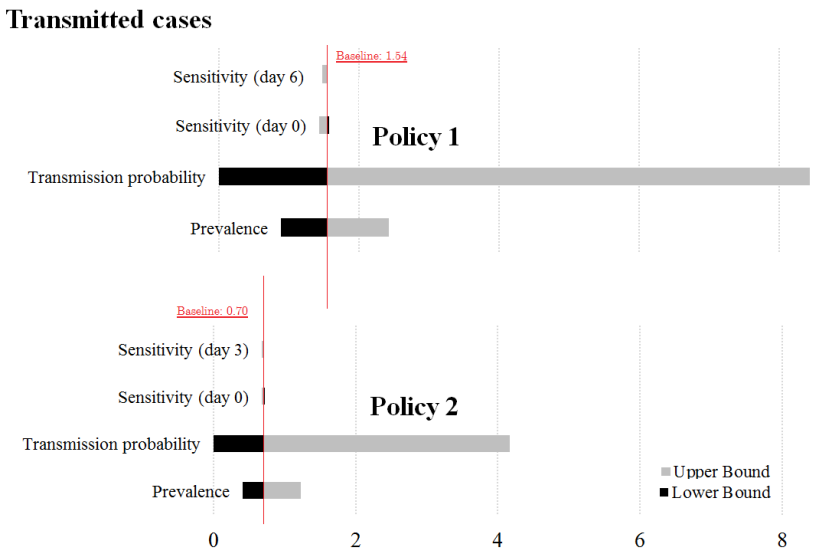

Figure 6.4: One-way sensitivity analysis and results comparison on the transmitted cases

6.4 Two-way sensitivity analysis

The one way sensitivity analysis indicates that Policy 2 would be more advantageous than Policy 1 in saving the total cost and the number of newly transmitted cases. However, when the transmission probability equals 0, the numbers of colonized (missed) cases from Policy 1 and 2 are very close; that is, if PCR sensitivity is lower than its baseline (57.0%) or culture sensitivity (day 6) is higher than 56.2%, Policy 2 could result in more missed or colonized cases than Policy 1. To examine when Policy 2 is appropriate to be implemented and when Policy 1 is more suitable for maximizing health outcomes, the two-way sensitivity analysis is conducted in this section.

Specifically, the analysis is applied by changing the transmission probability and the difference between PCR sensitivity (day3) and culture sensitivity (day 6), simultaneously. The measure of outcomes are the number of colonized and missed cases only since the total cost and the number of transmitted cases from Policy 2 are identifiably less than those from Policy 1 (due to the shorter isolation duration). Therefore, for each combination of a transmission probability and a difference between the screening sensitivities for Policy 1 and 2, we determine and compare the numbers of colonized and missed cases using the proposed simulation.

The difference between the screening sensitivities is generated by subtracting the culture and PCR sensitivities. For example, the lower bound of culture sensitivity is 49.5% and the upper

bound of PCR sensitivity is 62.0%, therefore, the lowest difference will be -12.5% (49.5%-62.0%). As the upper bound of culture sensitivity is 62.9% and the lower bound of PCR sensitivity is 52.0%, the highest difference will be 10.9% (62.9%-52.0%). Since both culture and PCR sensitivity range between the lower and the upper bound, other possible values of difference will fall in the range of -12.5% to 10.9% (Table 6.10).

The transmission probability under the base case is 0.0084 (in-isolation), which is calibrated according to the isolation effectiveness ratio of 3.154. The probabilities of 0.0108 and 0.0149 are the calibrated numbers under the effectiveness levels of 2.423 and 1.691, respectively (Table 3.4). In accompany with the exact probabilities from the literature, the representative combinations are presented in Table 6.10. Notice that the 0.048 is the transmission probability of not-in-isolation; however, the probability is utilized to represent the extreme cases where isolation is not effective.

6.4.1 Colonized cases

Table 6.10 shows the specific numbers of colonized cases under different combinations of transmission and sensitivity levels. For example, when culture sensitivity is 49.5% (lower bound of culture sensitivity at day 6) and PCR sensitivity is 57.0% (baseline sensitivity of PCR at day 3), the difference between the sensitivities is -7.5%. When a screening sensitivity holds constant, increasing the transmission probability will increase the number of colonized cases for both Policy 1 and Policy 2 simultaneously.

Table 6.10: Number of colonized cases under different combinations

Difference between sensitivities		Transmission Probability (in-isolation)						
		0	0.0013	0.0041	0.0084	0.0108	0.0149	0.048
-12.5%	cul 49.5%	22.54	22.77	23.33	24.15	24.59	25.51	31.80
	pcr 62.0%	22.15	22.26	22.61	22.95	23.26	23.62	26.69
-7.5%	cul 49.5%	22.54	22.77	23.33	24.15	24.59	25.51	31.80
	pcr 57.0%	22.18	22.27	22.77	23.20	23.52	23.90	26.95
-5.8%	cul 56.2%	22.21	22.45	22.98	23.93	24.36	25.21	31.49
	pcr 62.0%	22.15	22.26	22.61	22.95	23.26	23.62	26.69
-2.5%	cul 49.5%	22.54	22.77	23.33	24.15	24.59	25.51	31.80
	pcr 52.0%	22.44	22.52	22.83	23.32	23.71	24.05	27.27
-0.8%	cul 56.2%	22.21	22.32	22.98	23.93	24.36	25.21	31.49
	pcr 57.0%	22.18	22.27	22.77	23.20	23.52	23.90	26.95
0.9%	cul 62.9%	22.07	22.18	22.71	23.61	24.08	24.67	30.82
	pcr 62.0%	22.15	22.26	22.61	22.95	23.26	23.62	26.69
4.2%	cul 56.2%	22.21	22.45	22.98	23.93	24.36	25.21	31.49
	pcr 52.0%	22.44	22.52	22.83	23.32	23.71	24.05	27.27
5.9%	cul 62.9%	22.07	22.18	22.71	23.61	24.08	24.67	30.82
	pcr 57.0%	22.18	22.27	22.77	23.20	23.52	23.90	26.95
10.9%	cul 62.9%	22.07	22.18	22.71	23.61	24.08	24.67	30.82
	pcr 52.0%	22.44	22.52	22.83	23.32	23.71	24.05	27.27

Table 6.11: Difference between the colonized cases under different combinations

Difference between sensitivities	Transmission Probability (in-isolation)						
	0	0.0013	0.0041	0.0084	0.0108	0.0149	0.048
-12.5%	0.38	0.50	0.72	1.20	1.33	1.89	5.11
-7.5%	0.36	0.50	0.56	0.95	1.07	1.61	4.85
-5.8%	0.06	0.18	0.37	0.98	1.11	1.59	4.80
-2.5%	0.10	0.25	0.50	0.83	0.88	1.46	4.53
-0.8%	0.03	0.05	0.21	0.73	0.84	1.31	4.54
0.9%	-0.09	-0.08	0.10	0.66	0.83	1.05	4.13
4.2%	-0.22	-0.07	0.15	0.61	0.66	1.16	4.22
5.9%	-0.12	-0.09	-0.06	0.41	0.56	0.77	3.87
10.9 %	-0.37	-0.33	-0.13	0.29	0.38	0.62	3.55

To examine which policy is more advantageous under each combination, the difference between the number of colonized cases from Policy 1 and 2 is calculated with results shown in Table 6.11. For instance, when the transmission probability is 0 and the difference between the screening sensitivities is 4.2% (culture sensitivity is higher than PCR sensitivity by 4.2%); then, the difference between the number of colonized cases will be -0.07 (22.45 - 22.52) with the number colored by grey (Policy 1 has less number of colonized case). Similarly, for each subtracting result, if the number is less than 0, it will be colored with grey. Otherwise, the result will be left with white (Policy 2 has less number of colonized cases).

The white and grey colored numbers show the pattern of the difference in the number of colonized cases from Policy 1 and 2. When PCR sensitivity is higher than that of culture, the number of colonized cases from Policy 2 will be consistently lower than that from Policy 1. In such cases, as the transmission probability increases, the difference between the numbers of colonized cases increases.

However, when the culture sensitivity is higher, the number of colonized cases from Policy 2 will be more than that from Policy 1 when the transmission probability is low (grey colored); when the transmission probability is high enough, Policy 2 will generate less number of colonized cases. As the gap between the PCR and culture sensitivity becomes larger, the switching point from grey to white will show up later. For example, when the gap between the sensitivities is 0.9%, Policy 2 will have less number of colonized cases when the transmission probability is 0.0041 or higher; when the gap is large (i.e. 10.9%), Policy 2 will have less number of colonized cases when transmission probability is 0.0084 or higher.

6.4.2 Missed cases

The same analysis is conducted on the number of the missed cases because it is an important metric which is desired to be kept as low as possible. Table 6.12 provides the simulation results under each combination of the transmission probability and the difference between the culture and PCR sensitivities. Similarly, as the screening sensitivities remain constant, the more aggressive transmission will result in more number of missed cases. However, the pattern of the difference between the number of missed cases from Policy 1 and Policy 2 cannot be directly observed in the table. Therefore, Table 6.13 is introduced to clarify the pattern.

As it can be seen from Table 6.12, the number of the missed cases is continuously lower in Policy 2 when PCR sensitivity is greater than culture sensitivity; and the gap between the cases increases as the transmission probability rises.

However, given that the sensitivity of PCR is lower than that of culture, Policy 2 will produce more missed cases when the transmission probability is extremely low while the missed cases could be less when the transmission probability is high. Additionally, when the transmission probability is 0.48, the missed cases from Policy 2 will always be smaller than that from Policy 1.

Table 6.12: Number of missed cases under different combinations

Difference between sensitivities		Transmission Probability (in-isolation)						
		0	0.0013	0.0041	0.0084	0.0108	0.0149	0.048
-12.5%	cul 49.5%	7.57	7.70	8.04	8.44	8.72	9.28	12.49
	pcr 62.0%	5.77	5.85	5.90	6.02	6.11	6.25	7.40
-7.5%	cul 49.5%	7.57	7.70	8.04	8.44	8.72	9.28	12.57
	pcr 57.0%	6.50	6.58	6.71	6.91	7.03	7.23	8.45
-5.8%	cul 56.2%	6.51	6.61	6.91	7.30	7.56	7.97	10.69
	pcr 62.0%	5.77	5.85	5.90	6.02	6.11	6.25	7.40
-2.5%	cul 49.5%	7.57	7.70	8.04	8.44	8.72	9.28	12.49
	pcr 52.0%	7.36	7.40	7.48	7.69	7.85	8.02	9.52
-0.8%	cul 56.2%	6.51	6.66	6.91	7.30	7.56	7.97	10.69
	pcr 57.0%	6.50	6.58	6.71	6.91	7.03	7.23	8.45
0.9%	cul 62.9%	5.43	5.53	5.81	6.16	6.34	6.69	9.05
	pcr 62.0%	5.77	5.85	5.90	6.02	6.11	6.25	7.40
4.2%	cul 56.2%	6.51	6.61	6.91	7.30	7.56	7.97	10.69
	pcr 52.0%	7.36	7.40	7.48	7.69	7.85	8.02	9.52
5.9%	cul 62.9%	5.43	5.53	5.81	6.17	6.34	6.69	9.05
	pcr 57.0%	6.50	6.58	6.71	6.91	7.03	7.23	8.45
10.9%	cul 62.9%	5.43	5.53	5.81	6.17	6.34	6.69	9.05
	pcr 52.0%	7.36	7.40	7.48	7.69	7.85	8.02	9.52

Table 6.13: Difference between the missed cases under different combinations

Difference between sensitivities	Transmission Probability (in-isolation)						
	0	0.0013	0.0041	0.0084	0.0108	0.0149	0.048
-12.5%	1.80	1.86	2.14	2.42	2.61	3.03	5.09
-7.5%	1.07	1.13	1.33	1.53	1.70	2.05	4.12
-5.8%	0.74	0.76	1.00	1.28	1.45	1.72	3.29
-2.5%	0.21	0.31	0.56	0.75	0.88	1.27	2.97
-0.8%	0.01	0.08	0.20	0.39	0.53	0.74	2.24
0.9%	-0.34	-0.32	-0.09	0.14	0.23	0.43	1.65
4.2%	-0.86	-0.79	-0.58	-0.39	-0.29	-0.05	1.17
5.9%	-1.07	-1.05	-0.90	-0.74	-0.68	-0.55	0.60
10.9%	-1.94	-1.87	-1.67	-1.52	-1.50	-1.33	-0.47

6.5 The impact of T1 (day 0) screening

Ng et al. (2012) reported that the benefit of culture test at day 0 (T1 screening) is questionable due to the lower screening sensitivity. In order to test this claim, we defined Policy 3 and 4 as only PCR screening at day 3 and only culture test at day 6 (without culture test at day 0), respectively; and evaluated their performances using the proposed simulation model. Table 6.14 compares the performances of Policy 1 and 2 with Policy 3 and 4.

Table 6.14: Evaluating the impact of removing T1 (day 0) screening

	Policy 1	**Policy 2**	**Policy 3**	**Policy 4**
Day 0 screening?	yes	yes	no	no
Screening method	culture (day0 & 6)	culture (day 0) + PCR (day 3)	culture (day 6)	PCR (day 3)
Total Cost	$394,664	$246,408	$409,608	$249,253
Screening cost	$9,308	$16,635	$4,883	$12,654
Isolation cost	$288,052	$134,698	$302,557	$137,948
Colonization cost	$97,304	$95,076	$102,168	$98,651
Missed cases	7.30	6.91	10.90	10.43
Transmitted cases	1.54	0.7	2.11	0.99
Total colonized cases	23.93	23.20	25.24	24.19

Comparison of Policy 1 and Policy 3 shows that the removal of T1 screening (Policy 3) generates more number of missed and transmitted cases, as well as the total colonized cases. Therefore, Policy 3 is associated with higher isolation and colonization treatment costs compared to Policy 1, i.e., it increases isolation and colonization treatment costs by $4,868 and $14,505, respectively. Therefore, although the removal of T1 screening reduces the screening cost from $9,038 to $4,883, the total cost is increased by $14,944.

Likewise, removing the T1 screening from Policy 2 will result in similar outcomes (less screening cost but more total cost; more missed and transmitted cases; etc.) as removing the T1 screening from Policy 1. The experimental results from Policy 2 and Policy 4 show that the number of missed cases will increase from 6.91 to 10.43, the transmitted cases during isolation will go up from 0.70 to 0.99, and the total number of colonized cases will rise from 22.20 to 24.19 when the T1 screening is removed from Policy 1.

This analysis illustrated that administration T1 screening prior to both PCR testing at day 3 and culture testing at day 6 is cost saving. Thus, Ng et al. (2012)'s recommendation should be considered with caution.

6.6 Results of the robustness analysis

6.6.1 The number of colonized cases

Figure 6.5 and Table 6.15 show the policy comparison results of implementing the second screening by culture at day 6 with the second screening by PCR at day 1, 2, 3, 4, 5, and 6, respectively. Note that the lowest number of colonized cases under a particular transmission probability is highlighted with red in both Table 6.15 and Figure 6.5.

(1) When transmission probability equals 0, which means isolation is perfectly effective and no transmission is possible during isolation; then, screening at day 6 with PCR will result in the lowest number of colonized cases compared to the PCR screening at day 1, 2, 3, 4, or 5. In addition, this day 6 PCR screening has less number of colonized cases than culture screening at day 6 as the constant screening sensitivity of PCR (80.6%) is higher than that of culture (69.4%) among the detectable cases.

(2) When transmission probability equals the baseline value (0.0084), PCR screening at day 3 provides the lowest number of colonized cases; this outcome is consistent with the result from the previous analysis: Policy 2 has reduced number of colonized cases than Policy 1 (Section 6.1).

(3) When transmission probability equals the highest value within the literature (0.048), it is highly recommended that the colonized cases should be detected as early as possible; therefore, the lowest number of colonized cases comes from the PCR screening at day 1.

(4) In addition to the baseline, the least and the most aggressive transmission assumptions, the policies are compared under several transmission probabilities in between such as 0.006 (between

the lowest and the baseline) and 0.0149 (between the highest and the baseline). Results show that the optimal times of conducting the second time screening are day 5 and day 2 with PCR for the transmission probabilities of 0.006 and 0.0149, respectively.

As it can be seen, when transmission probability rises, it is preferable to diagnose the colonized cases earlier; however, when the probability is low, it is better to keep the roommates isolated and screened later since more colonized cases will become detectable as time increases.

Table 6.15: Colonized cases under different screening times and transmission levels

	P = 0	P = 0.006	P = 0.0084	P = 0.0149	P = 0.048
Culture (day 6)	22.22	23.34	23.79	24.98	31.56
PCR (day 1)	23.52	23.80	23.93	24.20	**25.84**
PCR (day 2)	22.76	23.13	23.27	**23.68**	26.00
PCR (day 3)	22.42	23.00	**23.16**	23.75	27.16
PCR (day 4)	22.20	22.93	23.22	24.05	27.99
PCR (day 5)	22.04	**22.90**	23.24	24.17	29.24
PCR (day 6)	**21.87**	22.94	23.31	24.45	30.16

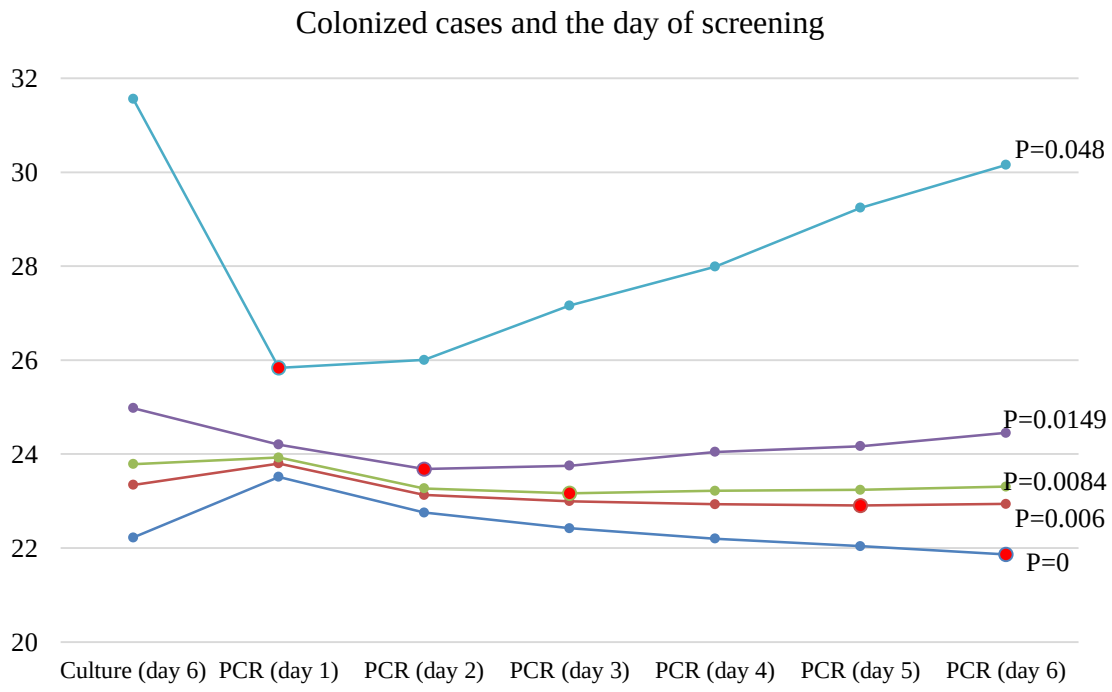

Figure 6.5: Colonized cases under different screening times and transmission levels

6.6.2 The total cost

The total costs from different policies under several transmission probabilities are presented in Table 6.16 and plotted in Figure 6.6 with the lowest cost highlighted with red under a particular transmission level.

As it is shown in Figure 6.6, under all transmission probabilities, PCR screening at day 1 and implementing 1-day isolation always provides the lowest total cost. Since isolation is expensive, the cost saved from other items (i.e. colonized cases, screenings) is not enough to offset the extra cost associated with longer isolation.

Table 6.16: Total cost under different screening times and transmission levels

	P = 0	P = 0.006	P = 0.0084	P = 0.0149	P = 0.048
Culture (day 6)	381,244	388,555	391,102	397,212	435,401
PCR (day 1)	**166,483**	**167,704**	**168,579**	**169,871**	**177,623**
PCR (day 2)	206,688	208,439	209,426	210,957	221,361
PCR (day 3)	242,487	245,293	246,060	249,657	266,782
PCR (day 4)	279,522	283,437	284,842	288,910	310,277
PCR (day 5)	314,577	319,920	321,482	327,221	353,918
PCR (day 6)	352,120	357,935	359,442	366,171	397,959

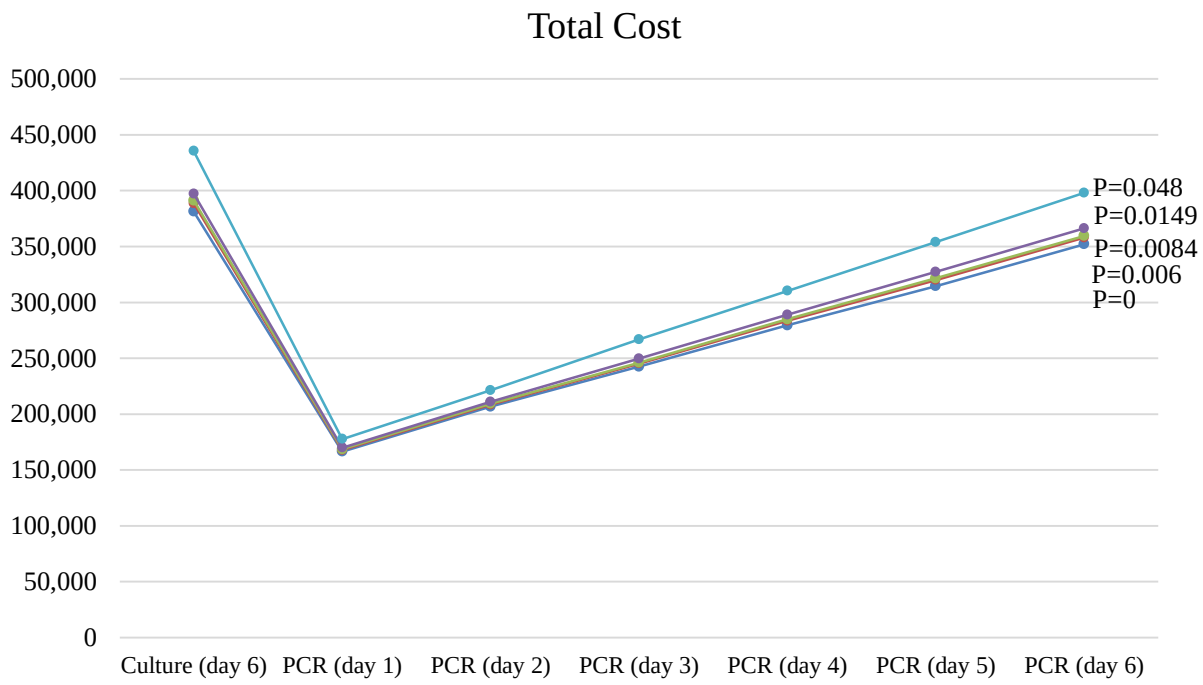

Figure 6.6: Total cost under different screening times and transmission levels

Chapter 7

Discussion

This chapter interprets the results obtained from Chapter 5 and discusses the reasonability and the impacts of the assumptions in the simulation models. In addition to the contents above, this chapter will also explain how the methodology can be applied in new situations.

7.1 Interpreting the results

7.1.1 Comparing the costs of the two policies

Results show that 72.9% of the total cost ($394,664/year) is caused by the isolation cost ($288,052) for Policy 1 while the isolation cost under Policy 2($134,698) constitutes 54.7% of the total expense ($246,408). The significant difference between the costs is caused by the variation of isolation duration. In Policy 1, approximately 97.6% of the exposed roommates are isolated for 7 days. For the proposed policy (Policy 2), these roommates will be isolated for 3 days only. Although Policy 2 and 1 leads to screening costs of $16,635 and $9,308, the isolation cost per day is far more expensive than the difference between the culture and PCR test costs. Therefore, the total economic cost of Policy 2 will be lower than that of Policy 1. However, the Policy 2 is not perfect; the major disadvantage of Policy 2 compared to Policy 1 is that Policy 2 results in higher number of false positives, which leads to an increased expenditures in isolation and screening procedures. Fortunately, only 2% of patients are diagnosed as false positive causing only a slight increase in the overall cost.

Sensitivity analysis confirmed that the total cost is most sensitive to the isolation cost under the existing policy; the prevalence and the cost of colonization are the second and the third largest contributor to the variation on the total expenses. It is clear that reducing the number of isolation days or the number of colonized cases would reduce the total cost dramatically. Since the prevalence is mainly deemed as an external factor that cannot be controlled within isolation directly, improving the effectiveness of isolation and detection will reduce the number of newly transmitted cases thereby providing lower total cost.

7.1.2 Comparing the colonized, missed, and the transmitted cases

The number of the colonized cases includes the patients who have already been colonized with MRSA (through the contact with the identified carrier before isolation starts) and the patients who become colonized during isolation. During the model calibration in Chapter 3, the total number of colonized cases is targeted as 8% of the patient cohort. This 8% should be distributed among the initial and the newly transmitted cases according to the isolation effectiveness ratio. The higher effectiveness ratio indicates less aggressive transmission (less newly transmitted cases) and the lower ratio means more aggressive transmissions (more newly transmitted cases) during isolation. Since the highest effectiveness ratio from the literature is selected as the base case scenario, the less aggressive transmission process is applied within the policy evaluation models in Chapter 4. This is a conservative assumption for the advantages of Policy 2: the results show that the proposed policy is superior to the existing one throughout all possible transmission probabilities when PCR sensitivity is higher than the culture sensitivity; when the sensitivity of PCR is less than that of culture, Policy 2 produces more number of colonized and missed cases than Policy 1 only if the transmission probability is very low. Therefore, the assumption of the less aggressive transmission for the base case will reduce the chance that the advantages of Policy 2 are over-estimated.

While longer isolation for all roommates provides higher probability for a colonized case to become detectable, it generally leads to more transmissions since it fails to diagnose the colonized ones earlier and keeps the patients with and without colonization stay in the same room longer. In contrast, PCR identifies the colonized cases rapidly and terminates the possible interaction between the colonized to the non-colonized cases at an early stage. However, when the transmission probability is much lower than the baseline (not a very realistic scenario) and the sensitivity of PCR (day 3) is lower than that of culture (day 6), very limited number of roommates will develop MRSA colonization during isolation; the benefits of PCR early detection and transmission termination cannot be justified in terms of the reduction in number of colonized and missed cases as Policy 2 leads to slightly more number of colonized and missed cases than Policy 1. Nevertheless, the increase in total number of colonized patients under Policy 2 is very small and it can be acceptable given the significant reduction in total cost of MRSA management among the exposed roommates. Thus, based on our assumptions, using PCR test at day 3 rather than culture at day 6 is preferable unless PCR is associated with significantly lower sensitivity than culture and when the transmission probability is very low.

The results are consistent with the study from Polisena et al. (2011), which concluded that the PCR rapid screening was less likely to spread MRSA. Our study shows that the number of newly transmitted cases during isolation is reduced by half when culture day 6 testing is replaced by PCR day 3 testing. Ng et al. (2012) mentioned that PCR screening might reduce the empirical isolation duration from 7 days to 3 days; our model implements the idea of reducing the duration and confirms the feasibility and the benefits from the shortened duration. Additionally, given the ongoing trend of MRSA in Canada (CNISP, 2011), more cost is expected to be saved under the proposed Policy.

7.1.3 The role of T1 screening

Results show that removing T1 screening reduces the cost involved in screening; however, the removal increases the number of colonized, missed, and newly transmitted cases, as well as the total cost. Although the sensitivity of culture at day 0 is much less than culture sensitivity at day 6 or PCR sensitivity at day 3, the benefit of having day 0 screening is more than just identifying some of the colonized cases at day 0, but also reduces the risk of the acquiring MRSA for the roommates remaining in the patient rooms as the transmission probability depends on the current number of colonized cases in a room.

7.1.4 The robustness analysis

Results from robustness analysis show that the optimal time of conducting the second screening (in terms of saving the number of colonized cases) switches from day 6 to day 1 as the transmission probability of in-isolation increases from 0 to 0.048. That is, when isolation is effective, it is better to keep the roommates isolated and screened later after the first screening; however, when isolation is not effective, it is more risky to put the non-colonized and the colonized patients together for long. Although longer isolation allows more colonized cases becoming detectable, it also leads to more transmitted cases; this is consistent with the results from the previous analysis. Therefore, the optimal time switches earlier as the transmission probability increases higher.

Interestingly, when both PCR and culture screening are conducted at day 6, PCR results in lower number of colonized cases. As both of the two methods are applied at day 6, theoretically, the same proportion of colonized cases will become detectable and screened with PCR or culture. Since the sensitivity of PCR (80.6%) is higher than that of culture (69.4%) for diagnosing the detectable cases, the missed cases will be reduced by PCR among the screened roommates.

Thereby, the total colonized cases will decline due to the reduced number of the missed-caused cases under PCR day-6 screening.

In terms of the cost, 1-day isolation always provides the lowest cost (not the lowest number of colonized cases unless the transmission probability of in-isolation is extremely high; i.e. 0.048). The cost of isolation is expensive and is counted in the number of patient-days; therefore, the cost of colonization may be slightly reduced as isolation duration increases, while the cost of isolation will increase dramatically. As a result, the shortest isolation leads to the least cost but not necessarily to the lowest number of colonized cases.

7.2 Limitation and assumptions

Ideally, a simulation model should comply with the hospital circumstance as much as possible in order to have a reasonable estimation of the unknown parameters, such as the prevalence level among the exposed roommates and the transmission probability within patients before and during the isolation. Therefore, having a good knowledge of MRSA screening and isolation procedures is critical to calibrate the model (Chapter 3) and evaluate the impact of the policies (Chapter 4) accurately. However, this study has a number of limitations. The categorized data collected from the literature and hospitals is limited and not detailed enough to clarify some missing information during simulation modeling; this study specifies such information via making assumptions.

7.2.1 Screening independency

The study is conducted based on the observational statistics provided by Ng et al. (2012). However, the paper does not specify which patient undergoes which screenings. For example, although results specifies how many roommates underwent day 0 culture test and day 3 PCR test, it does not specify how many patients underwent both day 0 culture and day 3 PCR test; in addition, it does not clarify whether a patient who has been screened previously (i.e. T1) would affect his or her screening decision in the next stage (i.e. T2 or T3).

Therefore, we assumed that patients are randomly selected to be screened in each time period of T1 to T3; that is, whether a patient has been screened in the precious time or not would not affect the screening process in the next time period. Additionally, patients who are screened at T2 are assumed to be tested with culture or PCR exclusively. However, the independency assumption might lead to a possible outcome that a patient is not screened at T1, T2, or T3 at all. Thus, the parameter estimation model insists that a patient who has never been screened in T1 or T2 be

screened at T3. Although this is a strong assumption, we had to make it as we did not have access to the detailed data from the North-York General Hospital.

7.2.2 Screening time

The paper mentioned the number of patients screened and the correspondent number of conversions found at T1, T2, and T3 screening. However, it does not specify the number of patients screened in a specific day (Di) and the number of conversions found from the Di screening. For example, the screening times are generally grouped into T1, T2, and T3 instead of the exact day 0, day 3, and day 7. Thus, 55% of the total conversions were detected in T2, which were the total numbers from day 2, 3, and 4 altogether. Likewise, 56% of the total conversions were detected in T3, which were the total numbers from day 5, 6, 7, 8, 9, and 10 altogether.

To estimate the sensitivity of culture and PCR objectively within the calibration model, the times of screening are assumed as follows: among patients who are screened in T1, which is day 0 to 1, each patient has equal probability of being screened at day 0 or day 1; among those who are screened in T2, each one of them has equal probability of being screened at day 2, 3, and 4. Similarly, a T3 screened patient has equal probability of being screened at any day of day 5 to 10.

7.2.3 Transmission probability

The transmission mechanism is assumed to be the same in North York General Hospital and Grand River Hospital. Several transmission assumptions have been made as follows: 1) all exposed roommates have the same probability of being MRSA colonized at the beginning of isolation; 2) a colonized case has the same probability of spread MRSA to each one of his or her roommates per day; 3) when a missed case is identified, this case will be deemed the same as a newly identified MRSA carrier, and contact precautions will be administrated to all roommates of the missed case as well; 4) MRSA transmission happens only among patients in the same room.

The transmission probability depends on how well the control practice is implemented and is also related to a patient's behavior. However, the two hospitals are fairly close geographically and the doctor confirms that the settings are almost the same in the hospitals. In addition, the transmission probability is adjusted according to the number of patients within a room and the amount of time they spent with each other. It is believed that the homogeneous assumption would not deviate from the reality to a significant level.

7.2.4 Isolation duration and discharging

The isolation duration and the discharging criteria are not clarified in the paper. Therefore, it is assumed that all roommates will stay in isolation until the completion of the last screening unless some of them have already been detected with MRSA positive from the previous screening(s); and the missed cases would stay in hospital continuously and be detected eventually.

It is unknown whether some patients are discharged from the hospital before isolation ends or some missed cases are identified after they are discharged from the hospital. When a discharge happens, the number of colonized and non-colonized patients and the transmission probability within a multi-bed room will change accordingly. Since 1) the "no discharging" assumption is applied for both the model of Policy 1 and Policy 2; 2) the majority of the cases have already colonized before they are isolated, the impact of the discharging will be offset when the policies are compared by the difference between the number of missed cases under Policy 1 and 2.

7.2.5 The probability of becoming detectable

Within the robustness analysis, the probability of transition from undetectable to detectable per colonized case per day is assumed to be a constant during isolation. However, as screening is not conducted every day within isolation, the stationary transition probability has to be added due to the lack of data.

7.2.6 The limitation of Arena

Arena is quite user-friendly software, however; it has several limitations. First, the running speed of Arena is not fast enough: a faster approach would reduce the time costs by the iterative calibration. For example, to estimate the unknown parameters in the parameter-estimation model in Chapter 3, both of the screening sensitivities and the transmission probabilities need to be adjusted; whenever the value of a parameter changes (i.e. culture sensitivity at T1), the model requires running for 500 replications which usually takes around 20-40 minutes (varies on different computers). However, if the running time of a 500-replication run can be reduced by half, the quality of calibration can be increased by running the model for 1000 replications without causing extra amount of time. Second, Arena is not a very flexible tool for extensive sensitivity analysis, e.g., to compare a model under different scenarios, the model has to be run manually for each scenario.

7.3 Incorporating the model in other hospitals

The model calibration is started from selecting an isolation effectiveness ratio *e*; thereby, model determines the number of already colonized patients before isolation and the number of patients becomes colonized during isolation. After the ratio is selected, the transmission probability of not-in-isolation is estimated by the conversion rate among each contact duration group, and the transmission probability of in-isolation is calculated by taking the division of the probability of not-in-isolation and the effectiveness ratio. Thereby, the unknown parameters can be estimated from the model calibration process by using the observable statistics provided from the literature or a hospital. Therefore, the application of the methodology in other situations can be achieved by considering the following aspects, which include 1) isolation effectiveness level; 2) the proportion of different contact durations; 3) the conversion rate from each contact duration group; 3) the room settings; and 4) the number of samples taken from the roommates.

7.3.1 Isolation effectiveness ratio

Since higher transmission probability might lead to an over-estimation of benefits from Policy 2, selecting a higher effectiveness ratio (lower transmission probability during isolation) will be a safe action in estimating benefits of the proposed policy.

7.3.2 Contact durations and conversion rates

The contact duration groups are probably not divided in the same way among different hospitals; correctly distinguishing the contact duration groups and the conversion rate within each group is essential in estimating the transmission probabilities and the total conversion rate. For example, North York reported that the conversions rates among patients who have contact duration less than 48 hours (Group 1), more than 48 hours (Group 2), and unknown duration (Group 3) are 0.058, 0.0114, and 0.133, respectively. Since the proportion of Group 1, 2, and 3 roommates are 62%, 36%, and 2% accordingly, the total conversion rate is calculated as:

$$0.058 \times 62\% + 0.114 \times 36\% + 0.133 \times 2\% = 8\%$$

It is clear that the rates are significantly different among groups and increasing the proportion of Group 1 will reduce overall colonized cases significantly. However, the duration groups can also be divided in different ways and the conversion rates among the groups will change. For instance, the Group 1 could be defined as patients who have contact duration more than 12 hours but less

than 24; Group 2 defined as patients who have contact duration more than 24 but less than 48, etc. Then, the conversion rate within each group will be less than 0.058 and 0.114.

7.3.3 Room settings and the samples

The room settings and the number of samples taken from the patients are the other two factors that need to be adjusted when the model is applied in other settings. Since the proportion of multi-bed rooms and the number of beds in a multi-bed room are probably different among hospitals, the number of patients within a room should be adjusted according to the room situations during the simulation modeling.

The number of samples taken from a roommate also depends on the hospital situation. For example, North York General Hospital conducts T2 screening but Grand River Hospital does not have. Whenever a positive case is identified from culture of PCR test, the patient will be moved out to the MRSA-positive room; thus, the screening reduces the risk of acquiring MRSA for the rest of the roommates in that room. Similarly, the number of patients in a room should also be adjusted when positive cases are identified.

To sum up, the structure of the parameter estimation and the policy evaluation model can be conserved, but the numerical parameters can be modified in order to tailoring the situations in other hospital.

Chapter 8

Conclusion

The main purpose of this study is to investigate the feasibility of implementing shorter isolation duration for the exposed roommates. The study first establishes a simulation model for estimating the unknown parameters (transmission probabilities and screening sensitivities) from model calibration; and then, the estimated parameters are utilized for comparing the performances of Policy 1, 2, 3, and 4 respectively. Finally, robustness analysis is developed by incorporating the detectability level of MRSA colonization in to the model. This analysis is used to measure the performances of administering PCR screening at day 1, 2, 3, 4, 5, and 6, as well as evaluating the performance of Policy 1 under the alternative assumption.

Results show that the accelerated detection of Policy 2 is consistently superior to Policy 1 in term of saving the total cost and the number of transmitted cases; the number of colonized cases and the missed cases are slightly reduced with PCR tests under the baseline assumptions. In addition, removing the T1 screening is not preferable as the total cost, the number of missed cases, colonized cases, and the transmitted cases will increase in Policy 3 and 4 comparing to Policy 1 and 2, respectively.

The one-way sensitivity analysis shows that both the number of colonized cases and missed cases are most sensitive to the prevalence and the transmission probability; however, the number of missed cases is more sensitive to the screening sensitivity than the number of the colonized cases. Thus, having lower sensitivity of PCR at day 3 compared to that of culture at day 6 may increase the number of the missed cases but not necessary increase the number of colonized cases. However, the one-way sensitivity analysis shows that when the transmission probability of in-isolation is extremely low (i.e. 0), the numbers of colonized and missed cases from Policy 1 and Policy 2 are very close. If the sensitivity of PCR at day 3 (culture at day 6) is lower (higher) than its baseline sensitivity value, it is not unlikely that these numbers from Policy 2 may be more than those from Policy 1. As a consequence, the two-way sensitivity analysis is implemented in searching under which combination of transmission probability and screening sensitivities, Policy 1 (7-day isolation) or Policy 2 (3-day isolation) is more preferable in saving the colonized cases and the missed cases.

Results from the two-way sensitivity analysis shows that the colonized cases and the missed cases will be reduced by Policy 2 when PCR sensitivity (day 3) is higher than culture sensitivity (day 6) throughout all transmission probabilities. Nevertheless, when the sensitivity of PCR at day 3 is lower than that of culture at day 6, Policy 2 will reduce the numbers of colonized and the missed cases when the transmission probability is higher than or close to the baseline (0.0084), while the numbers will increase when the probability is extremely low. Generally, as the number of newly transmitted cases from Policy 2 is always lower than that from Policy 1, if the transmitted cases saved from Policy 2 are capable of compensating the disadvantages caused by the lower sensitivity of PCR at day 3, then the total colonized cases will be less in Policy 2 than in Policy 1; otherwise, the colonized cases will be more in Policy 2.

In Chapter 3 and 4, the screening sensitivities are adjusted according to different sampling times. For example, the screening sensitivity of culture increases as the sampling time is postponed from T1 to T3. However, the robustness analysis assumes that the screening sensitivity of a method is constant at different days but the colonization level of a patient determines the detectability of the case. For instance, a patient's density of colonization might be too low to be detected at day 0, but will randomly become detectable at day 1, day 2, or day 3, etc. As the isolation days increases, an unknown case will become detectable with higher probability. Then, the impact of screening the roommates at day 1, 2, 3, 4, 5, and 6 can be evaluated respectively and the optimal time of screening can be calculated instead of focusing on day 3 for PCR and day 6 for culture testing only.

The robustness analysis confirms that PCR screening at day 3 results in both lower number of colonized cases and reduced cost of MRSA management than culture screening at day 6 as it is shown in the previous analysis; In addition, the robustness analysis shows that the early detection of MRSA would be more beneficial (i.e. lower total cost, less colonized cases) as the transmission probability increases during isolation. For example, the optimal screening time which gives the lowest number of colonized cases switches from day 6 to day 1 as the transmission probabilities increases from 0 to 0.048; meanwhile, the total cost reduces significantly as the isolation duration decreases by each time unit (by day). Note that a policy should be assessed in the combination of the total colonized cases as well as the total cost: when isolation is effective (*e* ratio is much higher than the baseline), isolation for longer will result in much higher cost but reduce the colonized cases.

References

Association, O. M. (2010, 11). *15*. Retrieved from Quality Management Program: Laboratory Services: http://www.qmpls.org/Portals/0/Newsletter/Archive/2010/qmplsnews156.pdf

Banks, J., Carson, II, J., Nelson, B., & Nicol, D. (2009). *Discrete-Event System Simulation, 5/E.* New Jersey: Prentice Hall.

Bracco, D., Dubois, M.-J., Bouali, R., & Eggimann, P. (2007). Single rooms may help to prevent nosocomial bloodstream infection and cross-transmission of methicillin-resistant Staphylococcus aureus in intensive care units. *Intensive Care Medicine, 33(5)*, 836-840.

Brown, J., & Paladino, J. (2010). Impact of Rapid Methicillin-Resistant Staphylococcus aureus Polymerase Chain Reaction Testing on Mortality and Cost Effectiveness in Hospitalized Patients with Bacteraemia. *Pharmacoeconomics, 28(7)*, 567-575.

Centers for Disease Control and Prevention. (2011). *Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Methicillin-Resistant Staphylococcus aureus.* Retrieved from Centers for Disease Control and Prevention: http://www.cdc.gov/abcs/reports-findings/survreports/mrsa11.pdf

Cepeda, J. A., Whitehouse, T., Cooper, B., Hails, J., Jones, K., Kwaku, F., . . . Wilson, A. P. (2005). Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: prospective two centre study. *The Lancet, 365(9456)*, 295-304.

Cheng, V., Tai, J., Chan, W., Lau, E., Chan, J., To, K., . . . Yuen, K. (2010). Sequential introduction of single room isolation and hand hygiene campaign in the control of methicillin-resistant Staphylococcus aureus in intensive care unit. *Bmc Infectious Diseases, 10(7)*, 263-272.

Evison J, M. K. (2008). Screening for carriage of methicillin-resistant Staphylococcus aureus shortly after exposure may lead to false-negative results. *Infect Control Hospital Epidemiology, 29(8)*, 774-776.

Forrester, M., & Pettitt, A. N. (n.d.). Use of Stochastic Epidemic Modeling to Quantify Transmission Rates of Colonization With MethicillinResistant in an Intensive Care Unit. *Infection Control and Hospital Epidemiology, 26(7)*, 598-606.

Hamel, M., Zoutman, D., & O'Callaghan, C. (2010). Exposure to hospital roommates as a risk factor for health care–associated infection. *AJIC: American Journal of Infection Control, 38(3)*, 173-181.

Harbarth, S., Masuet-aumatell, C., Schrenzel, J., Francois, P., Akakpo, C., Renzi, G., . . . Pittet, D.

(2006). Evaluation of rapid screening and pre-emptive contact isolation for detecting and controlling methicillin-resistant Staphylococcus aureus in critical care: an interventional cohort study. *Critical Care, 10(1)*, R25.

Jernigan, J. A., Titus, M. G., Gröschel, D. H., Getchell-white, S., & Farr, B. M. (1996). Effectiveness of contact isolation during a hospital outbreak of methicillin-resistant Staphylococcus aureus. *American Journal of Epidemiology, 143(5)*, 496-504.

Kelton, W., Sadowski, R., & Swets, N. (2010). *Simulation with Arena, 5th Edition.* New York: McGraw-Hill.

Kim, T., Oh, P. I., & Simor, A. E. (2001). The Economic Impact of MethicillinResistant in Canadian Hospitals. *Infection Control and Hospital Epidemiology, 22(2)*, 99-104.

Lee, B. Y., Song, Y., Mcglone, S. M., Bailey, R. R., Feura, J. M., Tai, J. H., . . . Piraino, B. (2011). The economic value of screening haemodialysis patients for methicillin-resistant Staphylococcus aureus in the USA. *Clinical Microbiology and Infection, 17(11)*, 1717-1726.

McGeer, A., Fleming, C., Willey, B., & Low, D. (2010, November). *Antimicrobial resistance in common hospital pathogens in Ontario.* Retrieved from Quality Management Program-Laboratory Services News: http://www.qmpls.org/Portals/0/Newsletter/Archive/2010/qmplsnews156.pdf

Moore C, D. J. (2008). Risk factors for methicillin-resistantStaphylococcus aureus (MRSA) acquisition in roommate contacts of patients colonized or infected with MRSA in an acute-care hospital. *Infection Control and Hospital Epidemiology, 29(7)*, 600-606.

Morgan, D. J., Diekema, D. J., Sepkowitz, K., & Perencevich, E. N. (2009). Adverse outcomes associated with Contact Precautions: a review of the literature. *American Journal of Infection Control, 37(2)*, 85-93.

Nelson, R. E., Samore, M. H., Smith, K. J., Harbarth, S., & Rubin, M. A. (2010). Cost-effectiveness of adding decolonization to a surveillance strategy of screening and isolation for methicillin-resistant Staphylococcus aureus carriers. *Clinical Microbiology and Infection, 16(12)*, 1740-1746.

Ng, W., George, K., Muhammed, N., Tomassi, J., & Katz, K. C. (2012). Too close for comfort: Screening strategy to detect methicillin-resistant Staphylococcus aureus conversion in exposed roommates. *AJIC: American Journal of Infection Control, 40(9)*, 883-885.

Nulens, E., Descheemaeker, P., Deurenberg, R., Stobberingh, E., & Gordts, B. (2010). Contribution of Two Molecular Assays as Compared to Selective Culture for MRSA Screening in a Low MRSA Prevalence Population. *Infection*, 98-101.

Nyman, J. A., Lees, C. H., Bockstedt, L. A., Filice, G. A., Lexau, C., Lesher, L. J., . . . Lynfield, R. (2011). Cost of screening intensive care unit patients for methicillin-resistant Staphylococcus aureus in hospitals. *AJIC: American Journal of Infection Control, 39(1)*, 27-34.

Papia, G., Louie, M., Tralla, A., Johnson, C., Collins, V., & Simor, A. E. (1999). Screening high-risk patients for methicillin-resistant Staphylococcus aureus on admission to the hospital: is it cost effective? *Infection Control and Hospital Epidemiology, 20(7)*, 473-477.

Pastagia, M., C., L., Kleinman, E. G., Cruz, L. d., & Jenkins, S. G. (2012, July). *Predicting Risk for Death from MRSA Bacteremia.* Retrieved from Centers for Disease Control and Prevention: http://wwwnc.cdc.gov/eid/article/18/7/pdfs/10-1371.pdf

Polisena, J., Chen, S., Cimon, K., Mcgill, S., Forward, K., & Gardam, M. (2011). Clinical effectiveness of rapid tests for methicillin resistant Staphylococcus aureus (MRSA) in hospitalized patients: a systematic review. *BMC Infectious Diseases, 11*, 336-336.

Provincial Infectious Diseases Advisory Committee. (2013). *Annex A: screening, testing and surveillance for antibiotic-resistant organisms (AROs).* Retrieved from Public Health Ontario: http://www.publichealthontario.ca/en/eRepository/PIDAC-IPC_Annex_A_Screening_Testing_Surveillance_AROs_2013.pdf

Public Health Agency of Canada. (2011). *Results of the surveillance of methicillin resistant staphylococcus aureus (from 1995 to 2009) A project of the Canadian nosocomial infection surveillance program (CNISP).* Retrieved from Public Health Agency of Canada: http://www.phac-aspc.gc.ca/nois-sinp/projects/res2009/pdf/res2009-eng.pdf

Raboud, J., Saskin, R., Simor, A., Loeb, M., Green, K., Low, D. E., & Mcgeer, A. (2005). Modeling Transmission of Methicillin-Resistant Staphylococcus aureus among Patients Admitted to a Hospital. *Infection Control and Hospital Epidemiology, 26(7)*, 607-615.

Robicsek, A., Beaumont, J. L., Paule, S. M., Hacek, D. M., Thomson, R. B., Kaul, K. L., . . . Peterson, L. R. (2008). Universal surveillance for methicillin-resistant Staphylococcus aureus in 3 affiliated hospitals. *Annals of Internal Medicine, 148(6)*, 409-418.

Rodríguez-Baño J, G. L. (2010). Long-Term Control of Endemic Hospital-Wide Methicillin-Resistant Staphylococcus aureus (MRSA): The Impact of Targeted Active Surveillance for MRSA in Patients and Healthcare Workers. *Infect Control Hosp Epidemiol, 31*(8), 786-795.

Rosner, A. J., Becker, D. L., Wong, A. H., Miller, E., & Conly, J. M. (2004). The costs and consequences of methicillin-resistant Staphylococcus aureus infection treatments in Canada. *The Canadian Journal of Infectious Diseases and Medical Microbiology, 15(4)*,

213-220.

Stelfox, H. T., Bates, D. W., & Redelmeier, D. A. (2003, Oct 8). Safety of patients isolated for infection control. *The Journal of the American Medical Association, 290(14)*, 1899-1905.

Tacconelli, E. A. (2012). The control of MRSA. In *Antibiotic Policies - Controlling Hospital Acquired Infection* (pp. 63-79). New York: Springer New York.

Tübbicke, A., Hübner, C., Hübner, N.-o., Wegner, C., Kramer, A., & Fleßa, S. (2012). Cost comparison of MRSA screening and management – a decision tree analysis. *BMC Health Services Research, 16(12)*, 438-438.

Tübbicke, A., Hübner, C., Kramer, A., Hübner, N.-O., & Fleßa, S. (2012). Transmission rates, screening methods and costs of MRSA—a systematic literature review related to the prevalence in Germany. *European Journal of Clinical Microbiology & Infectious Diseases, 31(10)*, 2497-2511.