

Optimizing Healthcare Delivery for Infectious Disease Testing

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

This thesis includes material from co-authored publications. Chapter 2 is based on the publication [Akgun et al. \(2023\)](#), and Chapter 3 is based on a submitted manuscript [Akgun et al. \(2024\)](#) co-authored by myself, my supervisors, Dr. Fatih Safa Erenay and Dr. Sibel Alumur Alev, and our collaborating clinical practitioner, William A. Ciccotelli from Grand River Hospital. Parts of Chapters 3 and 4 are also based on the publication [Lin et al. \(2023\)](#).

Abstract

Early detection of infectious diseases and isolation of the infected individuals are paramount for disease spread and controlling epidemics or pandemics. This can be achieved by timely testing of individuals at risk as part of secondary preventive care. Given the known effectiveness of screening and testing in the propagation of infectious diseases, testing operations should be planned and managed effectively. This thesis presents a series of novel mathematical models to optimize healthcare delivery for testing operations by addressing the unique characteristics of specific infectious diseases. The research focuses on two key applications: COVID-19 testing centers and MRSA surveillance testing protocols.

The first problem focuses on determining the locations and capacities of COVID-19 specimen collection centers to efficiently improve accessibility to polymerase chain reaction (PCR) testing during surges in testing demand. We develop a two-echelon multi-period location and capacity allocation model that determines the optimal number and locations of pop-up testing centers, capacities of the existing centers as well as assignments of demand regions to these centers, and centers to labs. The objective is to minimize the total number of delayed appointments and specimens subject to budget, capacity, and turnaround time constraints, which will in turn improve the accessibility to testing. We apply our model to a case study for locating COVID-19 testing centers in the Region of Waterloo, Canada using data from the Ontario Ministry of Health, public health databases, and medical literature. We also test the performance of the model under uncertain demand and analyze its outputs under various scenarios. Our analyses provide practical insights to the public health decision-makers on the timing of capacity expansions and the locations for the new pop-up centers. According to our results, the optimal strategy is to dynamically expand the existing specimen collection center capacities and prevent bottlenecks by locating pop-up facilities. The optimal locations of pop-ups are among the densely populated areas that are in proximity to the lab and a subset of those locations are selected with the changes in demand.

The second problem addresses surveillance protocols for hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). Roommates of nosocomial MRSA cases have a high risk of MRSA acquisition. Following infection prevention and control guidelines, these individuals are isolated and undergo surveillance testing. However, the optimal post-exposure surveillance testing and isolation strategies for contacts of index MRSA cases are unknown. We develop a Markov decision process (MDP) model to optimize the testing decisions for individuals exposed to MRSA cases in hospitals to minimize loss of quality-adjusted life years and number of MRSA colonizations. We solve the model optimally using data from clinical literature and conduct sensitivity analyses on key parameters,

including disutility values and disease parameters, such as prevalence and transmission probability. The optimal testing decisions recommend varying both the frequency and timing of tests based on initial test results and room configurations. Although implementing these optimal testing decisions may present challenges due to their complexity, they offer valuable insights for improving MRSA management in healthcare facilities, potentially leading to better health outcomes and cost savings compared to current guidelines and practices. We evaluate and compare the performances of various practical MRSA testing protocols, including different testing schedules and modalities using the proposed modeling framework enabling us to incorporate the test sensitivities on different days. We suggest alternative testing protocols with close-to-optimal performance that balances cost-effectiveness with clinical efficacy, aligned with decision-makers' objectives. Furthermore, the model's applicability extends beyond MRSA to other hospital-acquired infections with similar surveillance testing protocols, demonstrating its potential for infection prevention and control strategies.

The proposed MDP model helps identify the gap between optimal testing decisions, current practices, and alternative testing protocols. While it is effective for small and medium-sized hospitals, its scalability could be limited for larger institutions. To address this limitation, we propose a hybrid framework that integrates a Hidden Markov Model (HMM) with a discrete-event simulation (DES). The HMM mimics MRSA transmission and progression dynamics within isolated rooms, while the DES implements alternative testing protocols and reports related performance metrics. This hybrid framework provides computational efficiency for evaluating testing strategies in large healthcare settings. By incorporating varying test sensitivities for culture and PCR tests across different days, the proposed framework enables the evaluation of diverse MRSA surveillance testing protocols using hospital data and clinical literature. Furthermore, this approach allows us to address controversial policy questions related to MRSA testing strategies, such as the marginal benefit of day 0 testing, the ideal timing for initial and follow-up testing, and the most effective test modalities. Our analyses also identify the most effective testing protocols under specific parameter settings, which is particularly valuable given the significant variation in MRSA testing protocols across regions and institutions. By addressing these variations, the hybrid framework becomes a valuable tool for enhancing MRSA surveillance and supporting evidence-based decision-making in healthcare settings.

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Dedication

*This is dedicated to my parents—
my forever home, my childhood, and the source of unconditional love.*

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Chapter 1

Introduction

Healthcare management presents significant social and economic challenges for many countries due to its high expenditures and increasing demand. Problems related to the healthcare delivery systems have become much more important as the world's population is rapidly ageing, i.e., the proportion of people over the age of 60 is projected to nearly double, rising from 12% to 22% ([World Health Organization 2024](#)). As a result, healthcare systems are facing capacity issues as the demand for medical care is increasing. Alongside demographic changes, healthcare expenditure has also reached substantial levels, with many countries allocating a considerable percentage of their gross domestic product (GDP) to healthcare, e.g., 16.57% in the USA and 11.15% in Canada ([The World Bank 2024](#)). Therefore, the efficient allocation and effective management of healthcare resources will remain crucial to sustaining societal welfare and addressing the enduring challenges facing healthcare systems.

Healthcare problems have received considerable attention from the Operations Research (OR) community as OR provides many methodologies to address key healthcare problems including healthcare planning (e.g., demand forecasting, location selection, capacity planning), healthcare management and logistics (e.g., resource scheduling, logistics), healthcare practice (e.g., disease diagnosis, treatment planning), and specialized and preventive care (e.g., organ donation and transplant, vaccine selection) ([Rais and Viana 2011](#), [Batun and Begen 2013](#)). These problems are often complex, involving limited resources and multiple stakeholders with conflicting objectives. Providing effective and efficient solutions for these problems improves the quality of healthcare delivery while reducing the associated costs, which, in turn, alleviates the burden on the healthcare system economically, socially, and in terms of health outcomes. A substantial body of survey papers and book chapters further reviews OR applications in healthcare delivery ([Pierskalla and Brailer 1994](#), [Brandeau et al. 2004](#), [Rais and Viana 2011](#), [Zhang et al. 2011](#), [Batun and Begen 2013](#), [Kahraman and Topcu 2018](#), [Shetaban et al. 2020](#)).

Preventive care can save lives and improve quality of life by enabling disease prevention or treatment at earlier stages. Screening and testing operations are part of preventive healthcare facilitating early diagnosis and prompt intervention ([Verter and Zhang 2015](#), [Güneş and Örmeci 2018](#)). They play a vital role in managing both chronic and infectious diseases. Early detection of a chronic disease may save the life of an individual, reduce the impact of an existing disease or prevent future complications. On the other hand, early detection of an infectious disease and isolating the infected individuals prevents the spread of the disease to other individuals and helps to keep it under control ([Tejada et al. 2015](#)). Different modeling techniques are applied to a range of areas in disease diagnosis,

prevention, and control, including infectious diseases (e.g., influenza, HIV, COVID-19) (Yaesoubi and Cohen 2011a, Alistar et al. 2014, Shams Eddin et al. 2024) and chronic diseases (e.g., cancer, diabetes) (Denton et al. 2009, Ayvaci et al. 2012, Helmeczi et al. 2023).

Designing an effective screening program for a specific disease requires careful consideration of multiple factors. The screening test to be used, the timing of the screening, and the target population to be tested have to be determined in advance (Güneş and Örmeci 2018). Each factor points out a problem that has to be addressed. For instance, several screening methods should be evaluated and compared in terms of test specifications (sensitivity, specificity), cost and convenience to determine the best screening modality (Ayer et al. 2012, Ayvaci et al. 2012, Erenay et al. 2014). Additionally, factors related to the natural history of the disease such as prevalence and progression rate affect these decisions.

For modeling disease dynamics and concurrently analyzing screening policies, reliable estimation of the model parameters and making realistic assumptions are paramount to capturing the disease progression correctly (Tejada et al. 2015). This is because deriving the right insights depends on how well the model represents the real situation. Therefore, the data collection process and close collaboration with the clinicians and public health decision-makers as well as detailed analyses of the model outputs for the validation and verification of the models are important for designing effective screening policies with the help of realistic models.

Simulation models, Markov processes, Markov Decision Processes (MDPs), Partially Observable MDPs (POMDPs), and compartmental models are widely used to evaluate,

compare, and optimize screening policies while capturing disease dynamics and their impact on screening strategies (Steimle and Denton 2017, Güneş and Örmeci 2018, T. Denton 2023). Numerous studies have developed analytical models to optimize screening policies for chronic diseases, including cancer (Chhatwal et al. 2010, Ayer et al. 2012, Ayvaci et al. 2012, Erenay et al. 2014, Zhang et al. 2022b, Helmeczi et al. 2023, Li et al. 2023), diabetes (Denton et al. 2009, Kurt et al. 2011, Mason et al. 2012), and liver disease (Alagoz et al. 2004). However, research focused on optimizing testing protocols for infectious diseases is limited (Codella 2014, Song et al. 2024).

Developing an effective screening program alone is not sufficient for preventive care activities to be successful. The participation of people in these activities determines the effectiveness and success of the screening programs. Availability and accessibility are the main factors affecting people’s participation in screening operations (Zhang et al. 2010, 2012). Therefore, the effective planning and management of the delivery of screening operations are desirable to increase people’s participation and to ensure that screening operations serve the intended purpose. The main problems related to the management of screening delivery include the location of facilities, capacity planning, and allocation of available resources. OR techniques have been applied to address these problems as well. Several models are developed for the location and capacity allocation, and resource allocation problems in the context of screening operations. A comprehensive review of location models in preventive healthcare is provided in the book chapters by Verter and Zhang (2015), Güneş et al. (2019).

This thesis focuses on developing models to optimize healthcare delivery for infectious disease testing, providing solutions and insights that health clinicians and public health

policymakers can apply in practice. We study two applications, COVID-19 and MRSA surveillance testing, both of which highlight the critical role of early detection in preventing and controlling the spread of infectious diseases.

Chapter 2 addresses the problem of determining the optimal COVID-19 testing center locations and capacities. Several public health interventions have been applied to control the spread of disease and alleviate the burden since the beginning of the COVID-19 pandemic. Testing is one of the most effective interventions as it helps detect and isolate the infected cases and prevent the spread of the disease to other non-infected individuals. In this regard, the availability and accessibility of testing centers play a crucial role in testing operations to be successful. However, during periods of high demand, managing the testing operations becomes challenging due to limited capacities and longer turnaround times ([Brown 2020a,b](#)). To satisfy the increase in testing demand, the capacities of testing centers should be managed effectively by opening new testing centers or expanding the capacities of existing centers. In our work, we propose a two-echelon, multi-period location and capacity allocation model designed to reflect the COVID-19 testing system during the early stages of the pandemic in Ontario, Canada. We consider two different objective functions, providing flexibility based on the priorities and needs of the healthcare system and public health decision-makers. The first objective is to minimize the weighted sum of delayed appointments and specimens, while the second objective is to minimize total cost under a given acceptable value of delayed appointments and specimens, addressing budget constraints alongside maintaining service performance. We apply the model in a case study of the Region of Waterloo using real data. Our analyses demonstrate the potential of the proposed model and inform public health decision-makers on dynamic capacity

management of COVID-19 testing.

Chapter 3 and 4 investigate the surveillance testing problem for the exposed roommates of index Methicillin-resistant *Staphylococcus aureus* (MRSA) cases in a hospital. MRSA is a bacterial infection resistant to multiple antibiotics (Mayo Clinic 2020). MRSA infections, which may be acquired in healthcare facilities (HA-MRSA) or within the community (CA-MRSA), are particularly concerning in hospitals, where they significantly increase morbidity, mortality, length of stay, and healthcare costs (Lin et al. 2023). Studies show that MRSA infections are associated with a 20%-30% increase in mortality due to severe, often life-threatening complications such as sepsis (Kourtis et al. 2019). Our focus is on healthcare-associated MRSA, one of the most prevalent pathogens in hospital-acquired infection (HAI) models due to its substantial impact on patient outcomes and resource use. Infection Prevention and Control (IPAC) guidelines recommend testing patients upon admission and conducting targeted screening based on risk factors within healthcare facilities to prevent and mitigate the risk of transmission of an infectious disease (PHO 2023). When an individual is diagnosed with a hospital-acquired infection, such as MRSA, their roommates have a higher risk of colonization due to shared spaces and prolonged contact (Ng et al. 2012). These exposed individuals may cause further transmission if not identified and managed promptly, potentially leading to outbreaks and increased healthcare costs. According to IPAC guidelines, these individuals are isolated and undergo surveillance testing. However, the optimal isolation duration, the testing time, and the test modality are unknown.

In Chapter 3, we propose a finite horizon Markov decision process (MDP) model to decide on the optimal surveillance testing protocol for the exposed roommates of index

MRSA patients. Two different objective functions are proposed which are minimizing the loss of quality adjusted life years for exposed roommates and minimizing the number of cases colonized with MRSA. Since the true health states of the patients are unknown, and testing only provides partial information, the problem ideally requires a Partially Observable Markov Decision Process (POMDP) model. However, due to the computational challenges associated with solving POMDPs for large state spaces, we introduce a novel approach to model the problem as an MDP. The model is solved optimally using backward induction, with parameters derived from clinical literature and data provided by the Infection Prevention and Control (IPAC) department of Grand River Hospital. Our analyses provide insights for clinicians to improve the current practice for MRSA surveillance testing and identify practical MRSA testing protocols with close-to-optimal performance. The proposed model can be adapted for other hospital-acquired infections that follow similar testing and isolation protocols.

Chapter 4 introduces an hybrid framework with hidden Markov model (HMM) embedded discrete event simulation (DES) model to evaluate various MRSA surveillance testing and isolation protocols, considering different testing modalities, timings and intervals. The HMM-DES model addresses the scalability limitations of the MDP model proposed in Chapter 3 and provides a computational efficiency for larger hospital settings. In this framework, the HMM models MRSA transmission and progression among exposed roommates in isolated rooms, while the DES simulates the implementation of alternative testing protocols. The state definition of HMM allows for incorporating time-varying test sensitivities, enabling a more realistic representation of day-by-day testing accuracy. The HMM-DES model supports decision-making on testing and isolation protocols within a

hospital environment with different room types, including semi-private, cohort, and ward rooms. Through extensive numerical analyses, the model addresses several critical and controversial questions regarding MRSA testing protocols, exploring various disease transmission rates and test sensitivities. We identify testing protocols that are on the Pareto frontier, balancing total MRSA management costs against the number of MRSA colonizations and show that current practices can be improved by replacing culture test with a PCR test. Additionally, we determine the best testing protocol minimizing MRSA colonizations across different parameter settings, considering varying disease aggressiveness and test sensitivity levels.

The next three chapters of the thesis are self-contained, each presenting the motivation, detailed definitions of the specific problems studied, a review of the relevant literature, and the proposed models addressing these problems. The final chapter, Chapter 5, summarizes the key findings of each chapter, provides concluding remarks, and outlines potential directions for future research.

Chapter 2

Determining Optimal COVID-19 Testing Center Locations and Capacities

2.1 Introduction

The COVID-19 pandemic caused a significant burden to Canada with around 4,390,000 cases, 47,000 deaths, and \$275.2 billion expenditures as part of the COVID-19 economic response plan to date ([Government of Canada 2020](#)). Several public health interventions including vaccination, testing, contact tracing, isolation of infected cases, and social distancing measures have been applied to control the spread of disease, alleviate its burden, and efficiently manage the restricted healthcare resources to fight against the COVID-19

pandemic ([Barrett et al. 2020](#), [Campbell et al. 2020](#), [Tuite et al. 2020](#), [Li 2023](#)). COVID-19 testing and surveillance is a significant part of the effort to mitigate the transmission of the disease ([Campbell et al. 2020](#), [Manabe et al. 2020](#), [Cui et al. 2021](#)). The polymerase chain reaction (PCR) test is the gold standard in diagnosing not only COVID-19 but also several infectious diseases worldwide due to its high accuracy ([Zauli 2019](#), [Böger et al. 2021](#)). PCR testing facilitates early detection and timely isolation of COVID-19 cases, which reduces exposure of the public to the virus, and facilitates early treatment and appropriate contact management, which in turn limits disease propagation ([Manabe et al. 2020](#)). Therefore, testing is critical in every phase of the COVID-19 pandemic. The effectiveness of testing relies on fast access to testing facilities as participation in testing and surveillance depends on the accessibility to these facilities ([Verter and Zhang 2015](#)).

The COVID-19 testing demand changes over time depending on various factors including aggressiveness of the disease propagation, appearance of new variants, and effective implementation of public health interventions ([Tuite et al. 2020](#), [Barrett et al. 2020](#), [Miller 2022](#)). As observed in Ontario, during the peaks in the testing demand, the current capacity of testing centers and labs may not be sufficient to satisfy the demand ([Bueckert 2020](#)). These surges in the testing demand may lead to significant disruptions in the operations of testing centers causing longer test turnaround times and less effective COVID-19 mitigation ([Brown 2020a,b](#)). Therefore, determining the ideal level of testing capacity in line with the varying demand prevents long waiting times, improves turnaround times, and ensures the detection and isolation of infected individuals in a timely manner. This would, in return, provide more effective pandemic control.

In the early stages of the pandemic in Ontario, asymptomatic people could get tested

and there was a non-appointment-based testing system. However, with the rapid spread of the virus, the Ontario Ministry of Health (MOH), as of May 2020, prioritized those who are symptomatic or have been identified as a close contact of a confirmed case for COVID-19 testing ([Ontario Ministry of Health 2020](#)). In the summer of 2020, there was a decline in the number of COVID-19 cases and testing demand. However, with the beginning of fall, the symptoms of cold and influenza, which are similar to COVID-19 symptoms, have increased and caused significant surges in testing demand. Due to these significant surges, the capacities of the testing centers were overloaded and could not be managed well. For example, in September 2020, a drive-thru COVID-19 testing center in the city of Kitchener, Ontario was closed due to safety concerns. The cars and pedestrians waiting to get tested blocked the traffic causing a safety issue and the testing center was shut down for the day ([Brown 2020a](#)). In October 2020, Ontario transitioned to appointment-based testing ([Ontario Health 2020b](#)). The MOH continually updates the testing guidelines as the pandemic evolves ([Ontario Ministry of Health 2020](#)).

The capacity of COVID-19 testing is bounded by the limited number of healthcare personnel and their working hours ([Cui et al. 2021](#)). MOH has been increasing the testing capacity since the beginning of the pandemic based on the case count predictions from the statistical and epidemiological models developed by the Canadian COVID-19 modeling network ([Ogden et al. 2020](#)). For instance, in the first six months, testing capacity had increased from 4,000 to over 40,000 tests per day ([Ontario Health 2020b](#)). Although determining the ideal level of testing capacity in line with the varying demand is vital to use the available health resources effectively and flatten the curve, there is limited research addressing the question of when and where to implement these capacity increases.

In this chapter, we study the problem of determining the optimal COVID-19 testing center locations and capacities. We develop a mathematical model based on the current testing system in Ontario, Canada. We conduct a case study for the Region of Waterloo and perform various sensitivity analyses to demonstrate the potential of the developed model and to generate insights for the public health decision-makers on dynamic capacity management of COVID-19 testing.

The rest of the chapter is organized as follows. The next section presents the relevant literature to our problem. In Section 2.3, we describe the current system and define the problem. We introduce the notation and the mathematical formulation in Section 2.4. In Section 2.5, we present a case study, conduct numerical analyses using real data, and discuss the implications of our numerical analyses through sensitivity analysis. We present several managerial insights in Section 2.6. Finally, we provide concluding remarks and discuss future research directions in Section 2.7.

2.2 Literature review

Location problems in healthcare are well-studied in the literature ([Daskin and Dean 2004](#), [Ahmadi-Javid et al. 2017](#), [Güneş et al. 2019](#)). The objective functions of the healthcare facility location models depend on whose perspective is addressed as these decisions affect several stakeholders ([Batun and Begen 2013](#), [Güneş et al. 2019](#)). For instance, from the perspective of the patients, the main objective is to improve accessibility by minimizing travel costs or travel time, waiting time at the facility, or maximizing the quality of service ([Rais and Viana 2011](#), [Verter and Zhang 2015](#), [Güneş and Örmeci 2018](#), [Güneş et al.](#)

2019). On the other hand, the objective for the healthcare providers can be minimizing the operating and care costs as well as liability, while a societal perspective could consider several of these factors simultaneously (Güneş et al. 2019, Zhang et al. 2022a). The most common objective function for location problems in healthcare is the proximity of the facility to demand. Some of the other common and easy to quantify objective functions in the healthcare location literature are *i*) minimization of travel costs for healthcare consumers, *ii*) maximization of covered demand, and *iii*) maximization of equity in access (Güneş et al. 2019).

Ahmadi-Javid et al. (2017) classified healthcare facility location problems based on location management purposes into two main categories: non-emergency facilities and emergency facilities. According to this classification, the problem of locating COVID-19 testing centers falls under the category of non-emergency facilities and medical laboratories. Most of the papers related to non-emergency facility location problems are developed for locating primary care facilities (e.g., hospitals and clinics), and detection and prevention centers. Many of such studies focus on maximizing participation since early detection of a disease is very important for its prevention and management (Verter and Lapierre 2002, Zhang et al. 2009, 2010, Gu et al. 2010, Davari et al. 2015). There are a few papers in this domain that utilize an objective function for minimizing travel time or distance as well (Aboolian et al. 2012, Vidyarthi and Kuzgunkaya 2015). These models, however, are not applicable for locating testing centers to manage infectious diseases since they do not consider the dynamic nature of this decision problem which is essential to respond to varying demand over time due to disease propagation. On the other hand, there are studies that integrate COVID-19 testing decisions within an epidemiological framework considering

disease propagation and its effects on the demand, for example, by using compartmental models such as SEIR (Ogden et al. 2020, Tuite et al. 2020). However, those studies do not address the location and capacity expansion decisions for testing centers.

The location and capacity allocation decisions of medical laboratories and testing centers are critical in terms of infectious disease prevention, management, and control, and thus, for the promotion of public health and well-being. However, the research focusing on this area is very limited (Ahmadi-Javid et al. 2017). Saveh-Shemshaki et al. (2012) proposed a capacitated p -median location problem for designing a network of tuberculosis (TB) testing laboratories to minimize the total transportation times of the samples. They developed a facility location and capacity allocation model that determines the optimal locations and capacities of TB testing laboratories. Their objective is to minimize the total transportation time for the samples collected daily under the budget, capacity, and maximum transportation times between any origin and laboratory constraints. They implemented their model using the data for the TB reference laboratory in British Columbia, Canada. This model considers a single-echelon setting and does not allow for dynamic capacity expansion.

The demand is assumed to be stable in most healthcare facility location models. However, testing demand for infectious diseases, such as TB and COVID-19, varies significantly over time as disease prevalence changes. To capture the variations in demand, one needs to use dynamic models that allow making time-dependent decisions for the adjustment of capacities (Nickel and Saldanha-da Gama 2019). Jena et al. (2015) proposed a mixed-integer formulation for a generic dynamic facility location problem that allows modular capacity changes with the possibility of expansion and reduction as well as facility closing and

reopening. Only a few studies address dynamic aspects of the facility location problems for primary healthcare facilities ([Ndiaye and Alfares 2008](#), [Ghaderi and Jabalameli 2013](#), [Intrevado et al. 2019](#)) and vaccination sites ([Tang et al. 2022](#)) using multi-period models.

In this study, we also develop a multi-period facility location model. However, different from the other multi-period facility location studies or the literature on locating non-emergency facilities and medical laboratories, in our study, we consider the design of a two-echelon system where the flow coming into the facilities to be located (i.e., the demand of people to get their specimens collected), as well as the flow going out of the facilities (i.e., the specimens to be sent to labs for processing), are both important in terms of cost and processing times. Moreover, we model a different objective function that accounts for minimizing the weighted sum of delayed appointments and specimens and also incorporates constraints on the turnaround time which is imperative in testing infectious diseases.

The waiting time of specimens is an important factor that needs to be considered in the calculation of turnaround times. Our model considers both the waiting time of specimens after collection as well as the waiting time due to congestion at labs. Most studies on location of prevention centers incorporate congestion into their formulations using queuing models ([Zhang et al. 2009, 2010, 2012](#), [Dogan et al. 2019](#), [Ramirez-Nafarrate et al. 2015](#)). In our study, we model time delay due to congestion at the labs with a generic function that depends on the capacity utilization of each lab and incorporate this delay in processing times at the labs into the turnaround time constraint ([Alumur et al. 2018](#)). For computational efficiency, we then use a piecewise linear function to model the delay in processing times at the labs due to congestion as it is known that piecewise linear functions can be a reasonable approximation for non-linear functions ([Elhedhli and Hu 2005](#), [Elhedhli](#)

2006, Vidhyarthi and Kuzgunkaya 2015).

To the best of our knowledge, only a limited number of studies focus on locating COVID-19 testing centers (Liu et al. 2021, Li et al. 2022). Li et al. (2022) proposes a bi-objective parallel machine scheduling-location model to optimize the design of massive COVID-19 testing programs. The objectives of this model are to minimize the makespan and total traveling distance while determining the location of testing sites as well as assigning and scheduling the tested communities. The authors apply their model to real-world data from the city of Wuhan, China. The proposed model is not a multi-period model, hence, dynamic changes in the testing demand over time are not modeled. Zhang et al. (2022a) study a related problem on vaccination site selection, appointment acceptance and assignment, and scheduling decisions for mass vaccination. Liu et al. (2021) determines the locations of testing centers and dynamically adjusts their capacities for a case study in China, where these testing facilities can be opened only in the first period during the planning horizon. The COVID-19 testing system modeled in these existing studies is quite different than the integrated network in Ontario which requires a two-echelon structure and where testing capacity can be adjusted by expanding the capacities of the existing centers as well as by opening pop-ups over the entire planning horizon. Moreover, these studies do not incorporate constraints on test turnaround times nor consider congestion and delays in the facilities providing COVID-19 testing services.

To conclude, there is not any study in the literature that simultaneously addresses the dynamic aspect of location decisions in a two-echelon setting considering capacities, budget, congestion, and turnaround times. Hence, the developed model is different than the traditional facility location models as it incorporates several aspects that are specific

to the system being modeled.

2.3 System description and problem definition

Ontario’s public health system includes several provincial organizations and local public health units (PHUs) that work in collaboration as described in Figure 2.1. The MOH makes strategic decisions to promote and manage health care delivery and public health by developing legislation, regulations, and policies. The Ministry is responsible for funding and maintaining a sustainable health system by ensuring that it satisfies the needs of people in Ontario ([Public Health Ontario 2020](#)). Within the Ministry, the Office of Chief Medical Officer of Health (CMOH) identifies the provincial public health needs, determines the public health strategies, and controls the public health programs delivered by Ontario’s local PHUs. The CMOH reports directly to the Ontario Deputy Minister of Health. Based on the strategies and policies developed by the CMOH, PHUs provide an efficient community health program focusing on disease prevention, control of infectious diseases, and surveillance at the local level and lead to execute these provincial strategies. Public Health Ontario (PHO) provides scientific and technical information and expertise to MOH, CMOH, and local PHUs to help with their decisions and actions ([Public Health Ontario 2020](#)). Moreover, PHO conducts laboratory testing for several diseases and supports other organizations in Ontario’s public health system in case of an emergency or outbreak. Ontario Health (OH) helps create an integrated public health system for Ontario by coordinating and connecting the aforementioned provincial health agencies to ensure better health care delivery. Its main task is to oversee the health care system, suggest improve-

ments, and provide support for other agencies when needed (Public Health Ontario 2020).

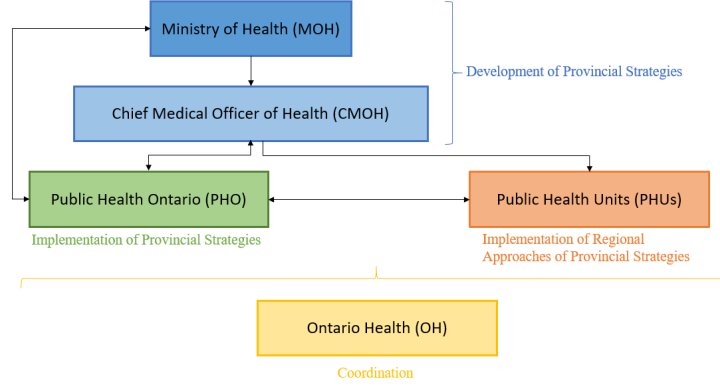


Figure 2.1: Overview of Ontario Public Health System.

As detailed above, there are several different stakeholders involved in the healthcare system of Ontario (i.e., MOH, CMOH, PHUs, PHO, and OH). COVID-19 testing is delivered through an integrated network via the collaboration of these stakeholders. Given the complex nature of the Ontario healthcare system, in the next subsection, we first present an overview of the system delivering COVID-19 testing and explain the roles of these different organizations in this process. We then define the problem on hand in Section 2.3.2.

2.3.1 Overview of the Current COVID-19 Testing Process

Ontario has developed the COVID-19 testing network to manage specimen collection, transportation and logistics, laboratory analysis, and reporting of the results. Figure 2.2 describes the structure of the COVID-19 testing network in Ontario. In this network, the MOH administers the overall testing strategy. By tracking the spread of COVID-19, MOH makes strategic decisions and deploys resources as needed. CMOH provides testing

guidance which is developed and updated based on the recommendations from a testing strategy expert panel coordinated by PHO. OH coordinates specimen collection, transportation and routing, lab processing, and reporting. OH also helps with the procurement of testing supplies and distribution of them to assessment centers and hospitals. In addition, OH works with the MOH to expand the provincial lab network's capacity. Lastly, PHUs handle contact tracing and case management. PHUs also help with the decisions regarding the assessment centers based on local needs (Ontario Health 2020a).

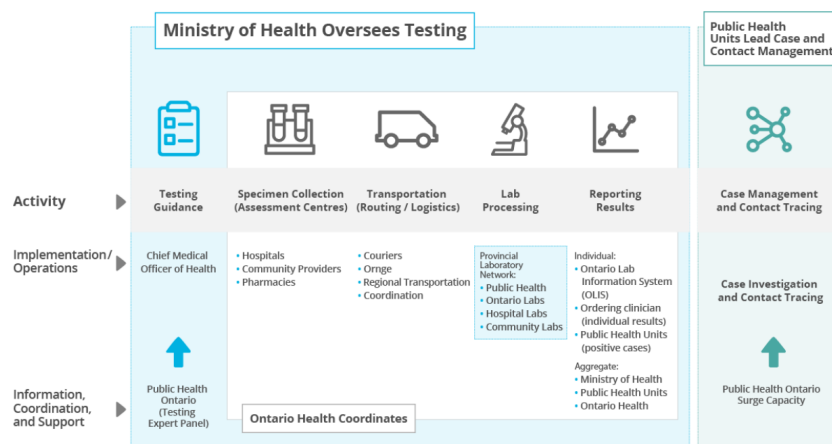


Figure 2.2: COVID-19 Testing Network in Ontario Ontario Health (2020a).

The process of COVID-19 testing for an individual patient or specimen in Ontario is explained in the process flow diagram depicted in Figure 2.3. The red dashed boxes in this figure represent the waiting times of individuals or specimens throughout the testing process. Specimens are collected from the individuals at *assessment centers*, which include hospitals, pharmacies, drive-thrus, and mobile pop-up centers. Since all assessment centers in Ontario serve by appointment only, the individuals who want to get tested first need to book an appointment through the web portal or by phone.

The specimens for PCR testing are collected from the individuals during their appointments at the assessment centers. After the collection, the specimens are sent from the assessment centers to the labs using couriers. The specimens from each assessment center are sent to a lab that is best positioned to analyze the results in a reasonable time, e.g., within two days. The specimens may need to wait at the assessment centers as they are sent to the lab in batches. The waiting time depends on how frequently the assessment center sends the collected specimens to the lab. The *turnaround time* of the specimens, which is the amount of time it takes for test results to be available after specimens are collected, varies based on the location and transportation schedule of assessment centers, proximity to the lab performing the PCR testing as well as the workload of the lab. The regional transportation coordination system organizes the routing and logistics across the province to achieve the targeted turnaround times.

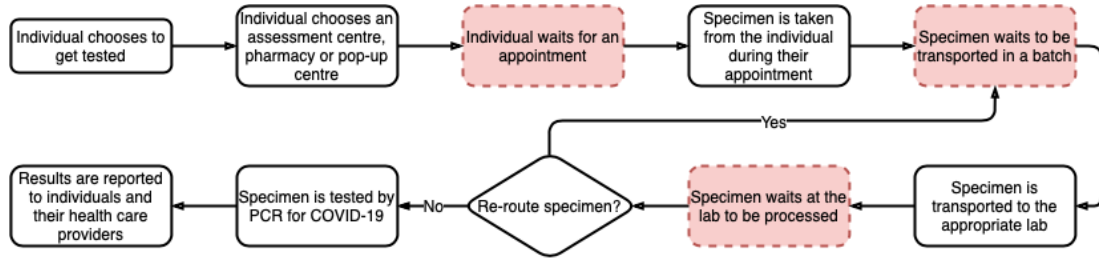


Figure 2.3: COVID-19 testing process flow diagram (red dashed boxes represent waiting times).

The specimens are analyzed within the provincial laboratory network consisting of PHO, hospital, and community labs. When the specimens arrive at a lab, they may wait to be processed depending on the congestion in the lab. However, if the lab is at its capacity, the specimens may be rerouted to another lab with available capacity. Therefore,

directing the specimens to the labs with sufficient capacity is important to balance the workload at the labs, limit the additional transportation cost, and reduce time spent due to the rerouting of the specimens, which may increase the turnaround times.

After the specimens are processed, the lab results are posted in the Ontario Lab Information System (OLIS) and become available in the Government of Ontario’s results portal for individuals and attending clinicians to access them confidentially ([Ontario Health 2020a](#)). If the test result is positive, it is shared with the local PHU, which initiates contact tracing and case management. OH coordinates this integrated system of specimen collection, transportation, lab processing, and reporting to provide timely turnarounds. Their aim is to achieve a target of delivering 80% of the test results within two days of specimen collection.

There are several potential issues related to the performance of the current system. During peak demand, the assessment centers may have insufficient specimen collection capacity (not enough appointments per day) which may cause delayed testing of individuals at risk and, in return, increased risk of spreading the virus. Such bottlenecks can be avoided by preemptively expanding the capacities of the existing centers or deploying additional pop-up testing centers. However, there is no systematic approach to determine when and where to deploy these pop-up centers and how much to increase the capacity of the existing ones.

Another important concern is related to the flow of specimens from assessment centers to the labs. There may be several labs that can be highly congested during peak demand times which would necessitate the rerouting of many specimens to other labs that may, in

turn, result in significant delays in the turnaround time. The rerouting of the specimens might be prevented by dynamically assigning assessment centers to the labs with available capacity and anticipating the effects of congestion on the turnaround time in advance. To address these issues, optimize flows, and reduce inefficiencies in this current system, we define and model a new multi-period location and capacity allocation problem as detailed in the next section.

2.3.2 Problem Definition

We consider a two-echelon facility location and capacity allocation problem that determines optimal locations and capacities of testing (assessment) centers in Ontario over a finite planning horizon. The model analyzes the province of Ontario as being separated into 523 forward sortation areas (FSAs); i.e., geographical units based on the first three characters in a Canadian postal code. Ontario has a total of 34 PHUs and each FSA is assigned to a local PHU. Each PHU contains and coordinates several assessment centers including hospitals, pharmacies, and drive-thrus that perform COVID-19 testing. Although a single FSA may include multiple assessment centers, we represent this situation in the model as if there exists a single assessment center with a capacity equal to the total capacity of the existing centers in that FSA.

We assume, as validated by the MOH, that assessment centers can collect specimens from FSAs contained in their PHUs. Collected specimens are then processed at the labs which belong to the COVID-19 provincial diagnostic network. Although some patients may prefer to travel to specimen collection centers offering an earlier appointment in other

PHUs, this effect would be negligible as our model aims to minimize the total number of delayed appointments.

During the peaks in the testing demand, the capacities of the assessment centers may be overloaded, and the testing demand may not be satisfied on time (i.e., the target turnaround time may be exceeded). This can be avoided by expanding the capacity of existing assessment centers or opening new pop-up centers. For the existing centers, the timing of the capacity expansions and the expanded capacities need to be decided. The capacity of the existing assessment centers can be increased by a certain percentage of the existing capacity selected from a discrete set of alternatives, e.g., 10% or 25% of their existing capacity.

For opening new pop-up centers, the locations of these centers have to be determined. MOH arrange pop-up testing centers to be opened temporarily to increase accessibility to testing during the peaks in the testing demand. These facilities are typically located in the parking lots of community centers and are housed in buses, with a standard number of public health workers, doctors, or nurses on staff. That is, each pop-up center's capacity is standard and fixed. However, pop-up testing centers can be opened and closed more than once during the planning horizon. Each FSA represents a candidate location for a pop-up testing center. MOH wants every FSA to have a testing center located within a reasonable distance (e.g., within walking distance for downtown Toronto, or within the same PHU).

In the multi-period setting, the planning horizon is assumed to be finite and divided into discrete and equally sized periods. The timings of the operations considered in the model (e.g., waiting time for transportation and test processing times) are measured in terms of the number of periods they take. The decisions of opening pop-up centers and

capacity expansion for the existing ones are implemented at the beginning of periods. In addition, the specimens are collected at the beginning and sent to the labs at the end of given periods.

The processing of the specimens, from collection to the compilation of the PCR test results, needs to be completed within a given turnaround time that includes transportation and waiting times, and other delays. In particular, since each assessment center sends its specimens to a particular lab at specific periods, specimens may need to wait at the assessment centers until they are sent to a lab. Moreover, the congestion at the labs might delay the processing of the specimens which might, in turn, affect the target turnaround times. Hence, the effect of congestion at labs is incorporated into the problem as well. To sum up, the turnaround times of the specimens depend on the waiting time at the assessment center, transportation time from the center to the lab, processing time at the lab, and delay in processing due to congestion at the lab.

We reasonably assume that the congestion level at each lab depends on the percentage utilization of its capacity. We additionally assume a first-in-first-out (FIFO) policy to serve the testing demand and process specimens, i.e., the delayed appointments and specimens are served or processed in the first successive available period. Accordingly, the waiting time to get an appointment is at most one period if there is enough capacity in the succeeding period.

The turnaround time, which is the amount of time it takes for the test results to be available after specimens are collected, does not consider the time between requesting an appointment and providing a sample for the PCR test. We incorporate this factor in the

objective function by minimizing the total number of delayed appointments and ensuring that the required capacity increases are done to minimize the time people wait until their sample is collected. Furthermore, as detailed in the previous section, there might be a delay in processing specimens at the labs. Therefore, for the objective function of our problem, we minimize the weighted sum of delayed appointments and specimens.

An alternative objective function is to find the minimum required budget to serve a specified demand level by limiting the total number of delayed appointments and specimens, which we also consider and model in this study. We would like to note that other alternative objective functions, such as minimizing the total waiting time or minimizing the maximum travel distance may be also applicable to the considered problem. However, the public decision-makers in our setting prefer to incorporate these performance metrics through a turnaround time and maximum travel distance constraint.

To conclude, these system dynamics and targets constitute a problem of determining *i*) the optimal number and locations of pop-up centers to open, *ii*) the capacities of existing assessment centers to be expanded, *iii*) assignment of demand regions to the assessment centers, and *iv*) the assignment of specimens to the labs to minimize the weighted sum of delayed appointments and specimens subject to capacity, budget, turnaround time, and maximum travel distance constraints.

2.4 Model Formulation

In this section, we first introduce the required parameters and decision variables and then present a mathematical formulation of the problem detailed in the previous section.

Sets

K : Set of PHUs.

I_k : Set of FSAs contained in PHU $k \in K$.

J_k^e : Set of locations of *existing* specimen collection centers under PHU $k \in K$.

J_k^n : Set of potential locations for *new* pop-up centers under PHU $k \in K$.

J_k : $J_k^e \cup J_k^n$.

L : Set of labs.

Q_j : Set of available capacity increments for existing center $j \in J_k^e$ (e.g., 10%, 25%, 50%).

T : Set of time periods in a discrete and finite planning horizon.

T_j : Set of time periods that the specimen collection center $j \in J_k$ sends the collected specimens to the lab, where $T_j \subseteq T$.

$\hat{T}_j$: $T_j \cup \{0\}$, where $\hat{T}_{j\tau}$ corresponds to the τ^{th} element of the set, $\tau = \{1, \dots, |\hat{T}_j|\}$.

Parameters

d_{it} : Testing demand of FSA $i \in I_k$ in period $t \in T$.

D_{jl} : Distance between specimen collection center $j \in J_k$ and lab $l \in L$.

L_k : Maximum travel distance for PHU $k \in K$.

C_{jt}^e : Capacity of the existing center located in $j \in J_k^e$ in period $t \in T$.

C_j^n : Capacity of the pop-up center to be located in $j \in J_k^n$.

- C_{lt} : Capacity of lab $l \in L$ in period $t \in T$.
- tp_l : Processing time of specimens in lab $l \in L$.
- t_{jl} : Transportation time of specimens from center $j \in J_k$ to lab $l \in L$.
- tw_{jt} : Maximum number of periods that specimens sent to a lab in period $t \in T_j$ wait in the collection center $j \in J_k$.
- Δ : Target turnaround time for specimens.
- $h(\cdot)$: Congestion function that represents the waiting time of the specimens at the lab.
- f_j : Fixed cost of operating a pop-up center in location $j \in J_k^n$ per period.
- g_{qjt} : Fixed cost of expanding the capacity of existing center $j \in J_k^e$ by $q \in Q_j$ in period $t \in T$.
- c : Variable operating cost of a testing center per person.
- v : Unit transportation cost of specimens from collection centers to labs (unit cost per distance).
- B : Available budget over the planning horizon.
- a_{ij} : Indicator specifying if center located in $j \in J_k$ can cover FSA $i \in I_k$, where
- $$a_{ij} = \begin{cases} 1, & \text{if } D_{ij} \leq L_k, k \in K, i \in I_k, j \in J_k, \\ 0, & \text{otherwise.} \end{cases}$$
- α : The weight of the total number of delayed appointments in the objective function.
- β : The weight of the total number of delayed specimens in the objective function.

Decision Variables

$$y_{jt} = \begin{cases} 1, & \text{if a pop-up center is opened in location } j \in J_k^n \text{ in period } t \in T, \\ 0, & \text{otherwise.} \end{cases}$$

$$z_{qjt} = \begin{cases} 1, & \text{if the capacity of existing center located in } j \in J_k^e \text{ is expanded by } q \in Q_j \\ & \text{in period } t \in T, \\ 0, & \text{otherwise.} \end{cases}$$

$$\omega_{jlt} = \begin{cases} 1, & \text{if center } j \in J_k \text{ sends specimens to lab } l \in L \text{ at the end of period } t \in T_j, \\ 0, & \text{otherwise.} \end{cases}$$

x_{ijt} = Number of people from FSA $i \in I_k$ served by specimen collection center $j \in J_k$ in period $t \in T$.

u_{jlt} = Number of specimens that is sent from center $j \in J_k$ to lab $l \in L$ at the end of period $t \in T_j$.

s_{it} = Number of delayed appointments from FSA $i \in I_k$ in period $t \in T$.

r_{lt} = Number of delayed specimens in lab $l \in L$ in period $t \in T$.

γ_{lt} = Capacity utilization rate of lab $l \in L$ in period $t \in T$.

Based on this notation, the mathematical model that minimizes the weighted sum of delayed appointments and specimens is formulated as follows:

$$\min \quad \alpha \sum_{k \in K} \sum_{i \in I_k} \sum_{t \in T} s_{it} + \beta \sum_{l \in L} \sum_{t \in T} r_{lt} \quad (2.1)$$

$$s.t. \quad s_{i(t-1)} + d_{it} = s_{it} + \sum_{j \in J_k} x_{ijt} \quad k \in K, i \in I_k, t \in T \quad (2.2)$$

$$x_{ijt} \leq a_{ij} d_{it} \quad k \in K, i \in I_k, j \in J_k, t \in T \quad (2.3)$$

$$\sum_{i \in I_k} x_{ijt} \leq C_j^n y_{jt} \quad k \in K, j \in J_k^n, t \in T \quad (2.4)$$

$$\sum_{i \in I_k} x_{ijt} \leq C_{jt}^e + \sum_{q \in Q_j} q C_{jt}^e z_{qjt} \quad k \in K, j \in J_k^e, t \in T \quad (2.5)$$

$$\sum_{q \in Q_j} z_{qjt} \leq 1 \quad k \in K, j \in J_k^e, t \in T \quad (2.6)$$

$$\sum_{i \in I_k} \sum_{t=\hat{T}_{j_\tau}+1}^{\hat{T}_{j_{(\tau+1)}}} x_{ijt} = \sum_{l \in L} u_{jl(\hat{T}_{j_{(\tau+1)}})} \quad k \in K, j \in J_k, \tau = \{1, \dots, |\hat{T}_j| - 1\} \quad (2.7)$$

$$\sum_{l \in L} \omega_{jlt} = 1 \quad k \in K, j \in J_k, t \in T_j \quad (2.8)$$

$$u_{jlt} \leq \mathcal{M} \omega_{jlt} \quad k \in K, j \in J_k, l \in L, t \in T_j \quad (2.9)$$

$$\sum_{k \in K} \sum_{j \in J_k} u_{jl(t-t_{jl})} + r_{l(t-1)} = C_{lt} \gamma_{lt} + r_{lt} \quad l \in L, t \in T \quad (2.10)$$

$$(tw_{jt} + t_{jl} + tp_l) \omega_{jlt} + h(\gamma_{l(t+t_{jl})}) \leq \Delta \quad k \in K, j \in J_k, l \in L, t \in T_j \quad (2.11)$$

$$\sum_{k \in K} \left(\sum_{t \in T} \left(\sum_{j \in J_k^n} f_j y_{jt} + \sum_{q \in Q_j} \sum_{j \in J_k^e} g_{qjt} z_{qjt} + \sum_{i \in I_k} \sum_{j \in J_k} c x_{ijt} \right) + \sum_{j \in J_k} \sum_{l \in L} \sum_{t \in T_j} v D_{jl} u_{jlt} \right) \leq B \quad (2.12)$$

$$y_{jt} \in \{0, 1\} \quad k \in K, j \in J_k^n, t \in T \quad (2.13)$$

$$z_{qjt} \in \{0, 1\} \quad k \in K, q \in Q_j, j \in J_k^e, t \in T \quad (2.14)$$

$$\omega_{jlt} \in \{0, 1\} \quad k \in K, j \in J_k, l \in L, t \in T_j \quad (2.15)$$

$$x_{ijt}, s_{it} \geq 0, \text{ integer} \quad k \in K, i \in I_k, j \in J_k, t \in T \quad (2.16)$$

$$u_{jlt} \geq 0, \text{ integer} \quad k \in K, j \in J_k, l \in L, t \in T_j \quad (2.17)$$

$$0 \leq \gamma_{lt} \leq 1 \quad l \in L, t \in T \quad (2.18)$$

The objective function (2.1) minimizes the weighted sum of the number of delayed appointments and delayed specimens over the planning horizon. Constraints (2.2) guarantee patient flow balance in consecutive periods. The sum of the number of delayed appointments from the previous period and the demand in the current period must be equal to the number of people who get tested plus the number of delayed appointments in the current period. Constraints (2.3) assure that people in each FSA can get tested only if there is a testing center within a certain travel distance. Constraints (2.4) and (2.5) are the capacity constraints for pop-up and existing specimen collection centers, respectively. Constraints (2.6) specifies that at most one capacity level can be selected for existing centers at each time period.

Constraints (2.7) ensure the flow balance of specimens between specimen collection centers and the labs. The total inflow which is the total number of specimens that are collected at a center must be equal to the total outflow which is the total number of specimens that are sent from that center to a lab at that time period. At the specimen collection centers, the specimens wait to be sent to a lab and the waiting time depends on the frequency that the center sends collected specimens to the lab. Thus, at each time period, the total number of specimens that are sent to the lab will be the sum of the specimens waiting until that time period.

Constraints (2.8) specify that each specimen collection center sends specimens to a single lab at each time period. Constraints (2.9) together with constraints (2.8) ensure that a specimen collection center does not send any specimen to a lab unless it sends all specimens to that lab. Constraints (2.10) ensure the specimen flow balance in consecutive periods at the labs. The sum of the total number of specimens that are sent to a lab and

the leftover specimens from the previous period must be equal to the sum of the processed and delayed specimens at that lab in the current period.

Constraints (2.11) make sure that the turnaround times of specimens do not exceed the target turnaround time. If a center sends its specimens to a lab, the sum of the waiting time of specimens at the center, transportation time to the lab, processing time at the lab and time delay due to congestion should not exceed the target turnaround time. Constraints (2.12) ensure that the total cost of operating pop-up centers, expanding the capacity of existing centers, the operational cost of testing and the transportation cost of specimens to the labs do not exceed the available budget. Finally, constraints (2.13)-(2.18) define the domains of the decision variables.

We would like to note that even though capacity expansion and pop-up location decisions are defined for each period, such an overly dynamic solution may not be easy to implement in practice. The model can readily be modified to ensure that capacity expansion or location decisions can be implemented only in certain periods. For example, those decisions can be defined in the first period of each day or only for specific periods, i.e., for a set of particular time periods that is a subset of T . Furthermore, if specific actions are not allowed for a certain PHU, FSA, or location, the values of the corresponding decision variables can be pre-set to zero before solving the model. Hence, the model is generic enough to accommodate such restrictions. We refer the readers to Section 5.2.4 for an analysis reporting the performance of a less dynamic and more practical form of testing decisions.

In the above model, in constraints (2.11), we use a non-decreasing generic congestion

function which depends on the capacity utilization at the lab. Let us now assume the congestion function $h(.)$ is a piecewise linear function specified by its breakpoints (b^m, δ^m) as shown in Figure 2.4. The capacity utilization of a lab can then be represented as a convex combination of two consecutive breakpoints (Elhedhli and Hu 2005, Elhedhli 2006, Vidyarthi and Kuzgunkaya 2015). The b^m and δ^m values can be obtained through expert opinion (as done in our case study) or by fitting a piecewise linear function to the actual congestion curve. To formulate the model using such a piecewise linear congestion function, we introduce the following additional notation:

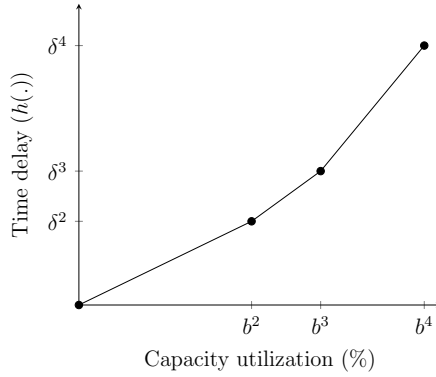


Figure 2.4: Piecewise linear congestion function.

M : Set of congestion levels considered for the labs.

b_l^m : Capacity utilization of lab $l \in L$ corresponding to the congestion level $m \in M$

(e.g., 80%, 100%).

δ_l^m : Waiting time of specimens in lab $l \in L$ corresponding to the congestion level $m \in M$.

In addition to the above parameters, we define a new set of binary variables and convex

combination multipliers:

$$\phi_{lt}^m = \begin{cases} 1, & \text{if utilization of lab } l \in L \text{ is between } b_l^m \text{ and } b_l^{(m+1)}, m \in M, \text{ in period } t \in T, \\ 0, & \text{otherwise.} \end{cases}$$

λ_{lt}^m = Convex combination multiplier corresponding to b_l^m for lab $l \in L, m \in M$ in period $t \in T$.

The model is then formulated as an MILP as follows:

$$\min \quad (2.1)$$

$$s.t. \quad (2.2) - (2.18)$$

$$\gamma_{lt} = \sum_{m \in M} \lambda_{lt}^m b_l^m \quad l \in L, t \in T \quad (2.19)$$

$$h(\gamma_{lt}) = \sum_{m \in M} \lambda_{lt}^m \delta_l^m \quad l \in L, t \in T \quad (2.20)$$

$$\sum_{m \in M} \lambda_{lt}^m = 1 \quad l \in L, t \in T \quad (2.21)$$

$$\lambda_{lt}^1 \leq \phi_{lt}^1 \quad l \in L, t \in T \quad (2.22)$$

$$\lambda_{lt}^m \leq \phi_{lt}^{(m-1)} + \phi_{lt}^{(m)} \quad l \in L, t \in T, m = 2, \dots, |M| - 1 \quad (2.23)$$

$$\lambda_{lt}^{|M|} \leq \phi_{lt}^{(|M|-1)} \quad l \in L, t \in T \quad (2.24)$$

$$\sum_{m=1}^{|M|-1} \phi_{lt}^m = 1 \quad l \in L, t \in T \quad (2.25)$$

$$\phi_{lt}^m \in \{0, 1\} \quad l \in L, t \in T, m = 1, \dots, |M| - 1 \quad (2.26)$$

$$\lambda_{lt}^m \geq 0 \quad l \in L, t \in T, m \in M \quad (2.27)$$

Constraints (2.19)-(2.25) determine two consecutive breakpoints of the congestion function that the capacity utilization of the lab lies between, and incorporate the corresponding time delay due to the congestion. Constraints (2.19) represent the utilization of lab capacity as a weighted average of breakpoints.

By constraints (2.20), the time delay corresponding to the congestion level at a lab is determined depending on the capacity utilization of that lab using the convex combination multipliers enforced by constraints (2.19). Constraints (2.21) ensure that multipliers add up to one. Constraints (2.22)-(2.25) impose the restrictions that all $\lambda_{lt}^m = 0$ except for one consecutive pair, i.e., λ_{lt}^m and λ_{lt}^{m+1} . Lastly, constraints (2.26) and (2.27) specify the domains of the variables.

Instead of introducing the binary variable ϕ_{lt}^m and constraints (2.22)-(2.26), we can define λ_{lt}^m as a special ordered set of type 2 (SOS2) variables which enforce that at most two λ_{lt}^m can be positive. We refer to the formulation with objective function (2.1), constraints (2.2)-(2.21), (2.27) and with SOS2 variables as the *min-delay* formulation.

The min-delay formulation minimizes the weighted sum of delayed appointments and specimens under a given budget. An alternative modeling approach is to find the minimum required budget to achieve a specific performance level in terms of targeted delayed appointments and specimens. In that case, the decision-maker needs to solve the model for given values of s_{it} and r_{lt} with the below objective function, which will be referred to as the *min-cost* formulation:

$$\min \sum_{k \in K} \left(\sum_{t \in T} \left(\sum_{j \in J_k^n} f_j y_{jt} + \sum_{q \in Q_j} \sum_{j \in J_k^e} g_{qjt} z_{qjt} + \sum_{i \in I_k} \sum_{j \in J_k} c x_{ijt} \right) + \sum_{j \in J_k} \sum_{l \in L} \sum_{t \in T_j} v D_{jl} u_{jlt} \right)$$

We develop two objective functions, i.e., *i*) minimizing a weighted sum of delayed appointments and specimens and *ii*) minimizing the total cost of designing and operating the testing system, and utilize them both in solving this problem. Both of these optimization problems are NP-hard as they can be reduced to the well-known *uncapacitated facility location problem* which is also NP-hard ([Garey and Johnson 1979](#)).

In particular, to solve our problem, we propose the following solution scheme. We first solve the min-delay formulation under a given budget and obtain the optimal values of the decision variables of the delayed appointments and specimens. Then, for these given values that are obtained by solving the min-delay model, say $\bar{s}_{it}$ and $\bar{r}_{lt}$, we solve the min-cost formulation to determine the minimum budget required to meet given values of delayed appointments and specimens. Alternatively, the two objective functions could be combined by incorporating a penalty cost for delayed appointments and specimens. The resulting problem can then be solved under a single objective function minimizing the total cost. In the next section, we present the application of the model in a case study from Ontario, Canada.

2.5 Computational Results

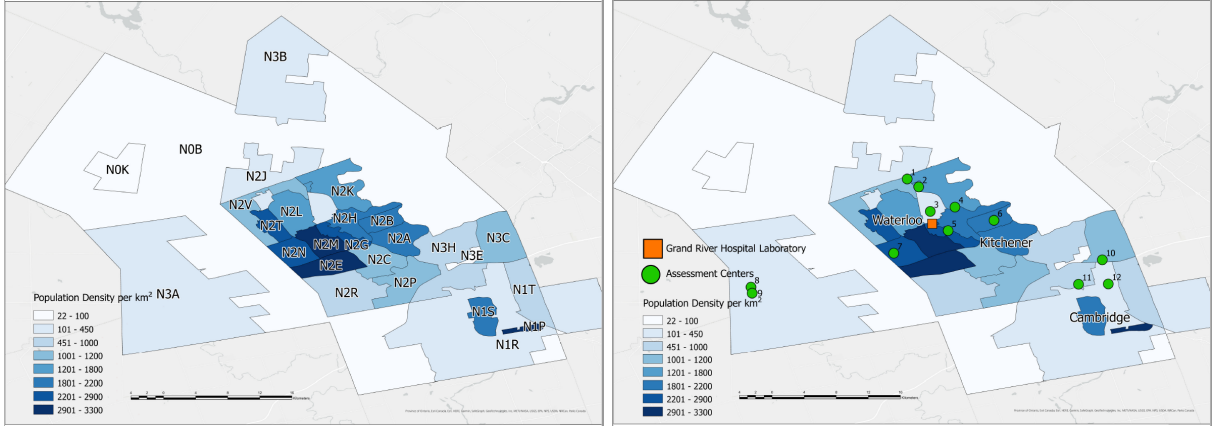
In our numerical analysis, we apply the developed model to facilitate access to COVID-19 testing in the Region of Waterloo (RoW) PHU in Ontario using real data and derive practical insights for the decisions and policies around the timing and locations of the required capacity expansions. All data regarding this case study is publicly shared ([Case study data 2022](#)). Throughout our computational analysis, we first solve the model with the

min-delay objective function using a loose budget constraint to obtain the minimum delayed appointments and specimens, and then minimize the required budget given these values. As there are enough potential sites for pop-ups and capacity expansion opportunities, we are able to obtain an optimal solution with no delayed appointments under a sufficient budget, i.e., $s_{it} = 0$ for all $i \in I$ and $t \in T$. In our analysis, we focus on finding the minimum required budget to ensure no delayed appointments unless stated otherwise. The mathematical model is solved using CPLEX 20.1.0 to optimality. All analyses are performed on a computer with a 2.3 GHz Intel processor and 8 GB RAM, running on macOS 10.15.7.

2.5.1 RoW Case Study

2.5.1.1 Input Parameters

The RoW is a mid-sized community including three cities located in southwestern Ontario (i.e., Cambridge, Kitchener, and Waterloo) with a population of around 630,000 people. Figure 2.5a shows the population density map of 26 FSAs in the RoW. Currently, the RoW has 12 assessment centers including hospitals (Grand River, St Mary’s General, and Cambridge Memorial Hospitals), drive-thrus, and pharmacies that perform COVID-19 testing in the PHU (Figure 2.5b). There is a single lab operated by the Grand River Hospital (GRH) that processes the specimens collected at the assessment centers. The frequencies of sending specimens to the labs, the congestion levels, the current capacities of the assessment centers and the lab are obtained through interviews with the public health officials from the RoW. We consider a one-week planning horizon divided into 4-



(a) FSAs in the Region of Waterloo.

(b) Assessment centers and the lab in the Region of Waterloo.

Figure 2.5: Locations of the FSAs, the assessment centers, and the lab in the RoW.

hour long periods. The one-week planning horizon is reflective of MOH's frequency of providing a report on COVID-19 assessment and reviewing the need for updating public health interventions ([Public Health Ontario 2022](#)). We assume that opening pop-up testing centers and capacity expansion decisions are made daily, i.e., at the beginning of each day. We assign a greater value to the delayed appointments in the objective function (i.e., $\alpha > 0.5$) to ensure no delayed appointments under the expanded testing capacity given a sufficient budget. The appropriateness of the planning horizon, frequency of the decisions, and weight values are approved by MOH.

We calculate the shortest traveling distances between FSA pairs using Python code and OpenStreetMap API. The maximum travel distance is taken as 20 km; i.e., there should be a testing center within 20 km of each FSA for individuals to get tested. Through our discussions with the MOH, we concur that 20 km is a reasonable maximum travel distance for RoW where parking spaces are widely available and affordable. The processing time of

specimens and target turnaround time are taken as 4 hours and 2 days, respectively, in line with the current practice ([Ontario Health 2020a](#)). We obtain the variable component of the operational cost from clinical studies estimating costs and human resources needed for several testing strategies ([Campbell et al. 2020](#)). Since some costs were confidential and are not publicly available, we estimate the fixed cost of operating pop-up testing centers and capacity expansion costs considering the capital cost of a mobile clinic and the salaries of the medical staff.

We derived the data on daily COVID-19 testing demand from the public reports of the MOH presenting the daily number of people tested in each PHU ([Government of Ontario 2020](#)). Since we consider FSAs in terms of the smallest geographic unit in our model, we assign each FSA’s testing demand proportional to its population. The appropriateness of this practice is also verified during our discussions with the MOH. Figure [2.6a](#) shows the 7-day averages of the number of tests completed in the RoW PHU over a year. To analyze the model outcomes under different demand scenarios, we choose three separate weeks each from December 2020, April 2021, and August 2021 that correspond to high, medium, and low demand intervals, respectively. The corresponding demand values for these three different weeks are shown in Figure [2.6b](#).

2.5.1.2 Case Study Results

We solve the model using the parameters introduced in the previous section for three different demand levels. Figure [2.7a–2.7c](#) presents the maps indicating the optimal locations and timing of required capacity expansions to satisfy all testing demand on time for high,

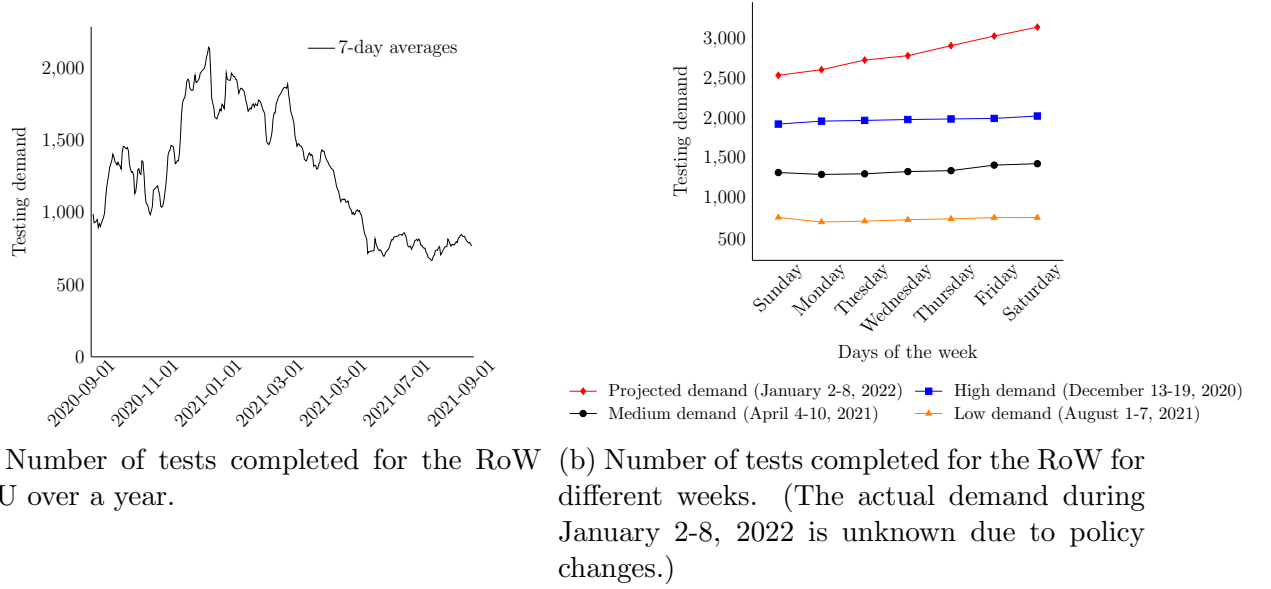


Figure 2.6: Testing demand for the RoW.

medium, and low demand weeks, respectively, based on the model solutions. The legends of the maps show the timing of the capacity adjustments. For instance, for the medium-demand week in April, the model suggests opening two pop-up testing centers one in N2C and the other in N2G, where the second one is not operated on Thursday.

Figure 2.7 shows that the developed model locates pop-up testing centers close to the lab to reduce the transportation cost of specimens from the assessment centers to the lab. Most of the capacity expansions are in existing centers located in densely populated areas that are close to the lab due to the same reason. The model dynamically changes the capacities of the existing centers to address the slight increases in demand at a minimum cost. In addition, the model opens pop-up centers in the south, southwest, and southeast sides of the lab (see Figure 2.7a). The first two location choices may be related to high population intensity in those sections of the regions (i.e., around FSAs N2M and N2G).

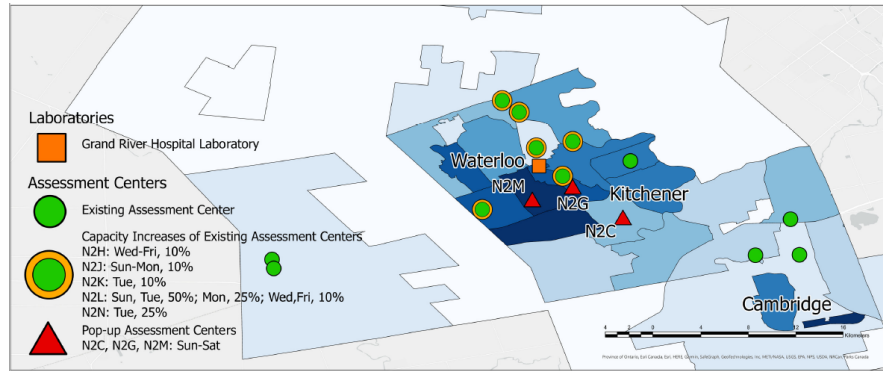
The last one could be explained by the lack of an existing assessment center to serve the medium-populated area between the southeast side of the lab and the city of Cambridge. Those insights are verified under higher demand scenarios as well (see Figure 2.8).

Another vital observation from Figure 2.7 is that, for the medium and low demand weeks, only a subset of the pop-up centers selected in the high demand week was opened. This indicates the possibility that varying demand would only change the number of additional pop-up centers to be opened and not their locations. Based on this observation, the RoW PHU can determine a set of stable pop-up center locations to be opened/closed depending on the pandemic load.

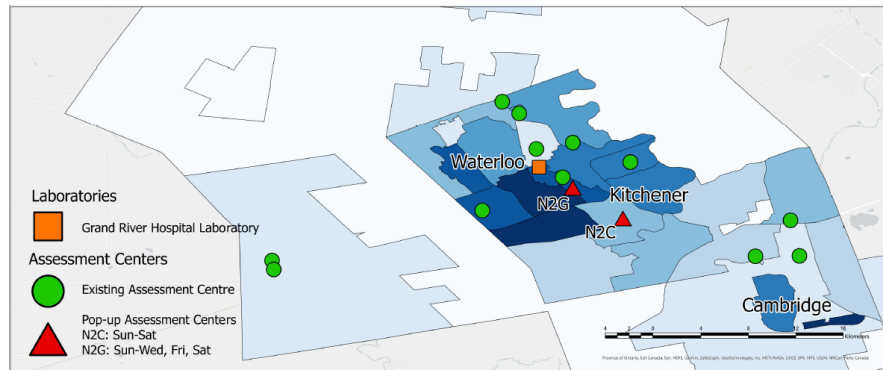
To test everybody in the medium and low demand week, the need for the capacity increase is addressed only through the use of pop-up centers. The model prefers opening pop-up testing centers rather than expanding the capacity of the existing ones due to the lower unit cost of testing at pop-ups; i.e., the unit cost of opening a pop-up testing center is lower than the unit cost of expanding the capacity of an existing one. For instance, for the high demand week, 49.2% of testing demand is satisfied by pop-up centers while only 2.1% is satisfied by the capacity increase in the existing centers.

2.5.1.3 Case Study with Projected Demand

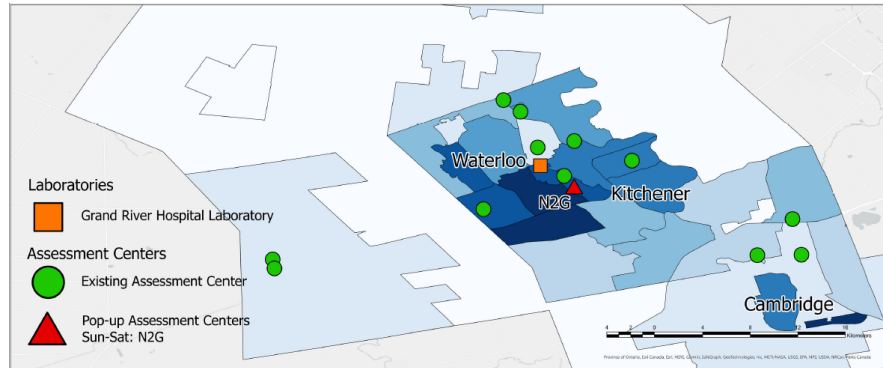
Although we evaluate the performance of the developed model retrospectively based on realized demand, the model can be used for prospective analysis with forecasted testing demand. To illustrate the potential of the model for prospective analysis, we focus on the post-Omicron period of the pandemic, which provides an ideal scenario for evaluating



(a) High demand week (December 13-19, 2020)



(b) Medium demand week (April 4-10, 2021)



(c) Low demand week (August 1-7, 2021)

Figure 2.7: The optimal locations and timings of capacity expansions for high, medium, and low demand weeks.

the extreme demand case. Following the emergence of the Omicron variant, the burden of COVID-19 on the health system has reached its highest levels since the beginning of the pandemic ([Baker 2022](#)). As a result, the significant increase in the workload on the assessment centers overloaded the existing capacities and individuals could not book a COVID-19 test appointment promptly ([DeClerq 2021](#)).

During this period, Canada has lost sight of the true size of the pandemic as the highly infectious Omicron variant overwhelmed the testing capacity ([Miller 2022](#)). MOH updated the guidance on PCR testing for COVID-19. Due to an unprecedented case volume and limited testing capacity, PCR testing was prioritized for those most vulnerable to COVID-19. A large portion of mild cases and exposures could not be tested, and these cases were not recorded. This eventually led to discrepancies in the reported numbers and real-time data. Since testing numbers can no longer be relied upon to accurately reflect the case count of COVID-19 in Ontario, we project the demand for testing using a forecasting model and analyze the continuation of PCR testing for everyone.

We developed an autoregressive integrated moving average (ARIMA) model to forecast the testing demand for the RoW after the emergence of the Omicron variant. ARIMA is a forecasting model that uses time-series data to predict the future values in the series ([Schaffer et al. 2021](#)). We built the ARIMA model in Python using the historical data from November 1 until December 24 as the transmission of the Omicron variant in Ontario was high during that time and forecasted the testing demand for the week of January 2, 2022. The projected demand values are shown in Figure [2.6b](#) in comparison to the demand patterns used in the previous analyses (low, medium, high). We then solve the developed model using the projected demand values to evaluate the model performance under an

extreme case. The locations and timings of capacity expansions required to test everybody on time with the projected demand values are presented in Figure 2.8.

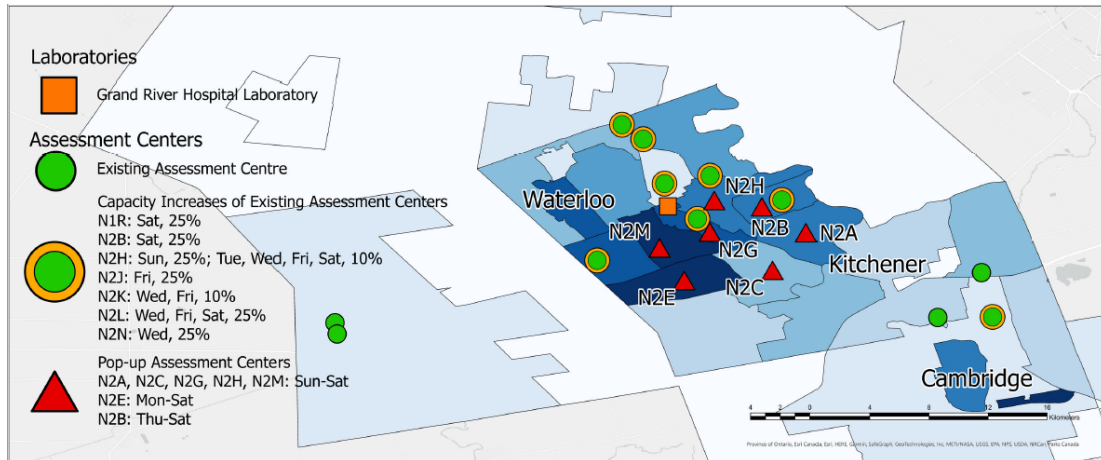


Figure 2.8: The locations and timings of capacity expansions with the projected demand values.

With the surge in the number of cases due to the Omicron variant, the model assigned more than twice as many pop-up centers to the RoW as it does for the high demand scenario in December (see Figure 2.8). Similarly, the capacity expansion for the existing testing centers is also much higher in Figure 2.8 compared to those in Figure 2.7. Like those in Figure 2.7, the model opened pop-up assessment centers around the lab to reduce transportation costs and better serve the highly populated areas around the lab. The majority of pop-up centers are opened in the south of the lab because there are no existing assessment centers on that side of the region except three assessment centers way down southeast around the city of Cambridge. The model did not open any new locations to the north of the lab as the capacities of existing centers are enough to cover the demand there.

Unlike the capacity expansion plans for the base case, the model outcomes propose a more composite plan dynamically utilizing pop-up centers and capacity expansion in

existing centers at a higher level than for the high demand case of December. To cover the majority of the demand during this interval, the model first opens five pop-up centers on Sunday and uses a 25% capacity expansion of the existing assessment centers to cover the residual demand. To address the increasing demand, the model opened an additional pop-up center on Monday and increased the capacities in several existing centers until Thursday. After that, since they become costlier, the model reduced the capacity expansions and opened an additional pop-up center instead. Figure 2.8 verifies our earlier observation that the pop-up locations at lower demand scenarios are subsets of those for higher demand scenarios, i.e., the pop-up centers opened for the high demand case of December 2020 are also opened for the extreme demand scenario of January 2022.

2.5.1.4 Case Study with Uncertain Demand

Although the developed model assumes that the testing demand over the planning horizon is known, it reflects the current decision-making process in the MOH. Public health decision-makers make capacity decisions periodically for upcoming weeks, as formulated in our model, using the projected demand values obtained from epidemiological models following a rolling horizon approach (Tuite et al. 2020, Ogden et al. 2020). However, the actual demand is unknown, thus, the performance of the actual and proposed capacity expansion plans may suffer from this uncertain nature of the pandemic. Therefore, we would like to evaluate the performance of our model under uncertainty.

For this purpose, we first solve our model using projected demand values and then evaluate the resulting solutions under the realized demand. In particular, we first forecast

the testing demand for high, medium, and low demand weeks using the ARIMA model based on testing demand of the preceding 8 weeks as described in Section 2.5.1.3. We then solve the developed model using these projected demand values to find the optimal pop-up locations and required capacity increases to test everybody on time. Next, we fix the optimal locations and capacity decisions obtained under the projected demand and evaluate whether the decisions of the proposed model are still effective under the realized demand. The results are presented in Table 2.1.

Table 2.1: Model outputs under projected and realized demand scenarios.

Demand set	Scenario	Total demand	Delayed appointments (%)	Avg utilization of pop-ups (%)	Avg utilization of existing centers (%)	Total cost(\$)
December (high)	Projected	13,631	0.0	81.5	68.8	843,572
	Realized	13,933	0.0	81.8	74.9	861,302
April (medium)	Projected	8,677	0.0	78.1	45.9	537,038
	Realized	9,508	0.0	74.7	55.5	585,760
August (low)	Projected	5,414	0.0	89.6	38.5	331,348
	Realized	5,231	0.0	89.8	36.5	320,672

In Table 2.1, the rows labeled as “Projected” present the outcomes of the optimal model using projected demand values from the ARIMA model. On the other hand, the performance metrics in rows labeled as “Realized” are obtained by minimizing the total cost under the realized demand where the timing and locations of capacity expansions are set to those obtained from the optimal solution using the projected demand values. The third column of the table presents the total demand values for both the projected and realized demand corresponding to each week. The performances are compared based on the percentage of the population whose appointments are delayed to the next day, utilization of testing resources, and total cost.

Table 2.1 illustrates that the projected and realized performances are very close to

each other. Specifically, when the plan with projected data is applied under the realized demand, it still guarantees timely service of all testing demand, i.e., zero percent delayed appointments, in all three demand sets. The deviation of the actual demand from the projected values results in small differences in the average utilization of pop-ups and existing centers and the total cost. In high and medium demand weeks, the average utilization rate and total cost evaluated using the realized demand values are higher than those for the projected demand because the realized demand during these weeks exceeds the projected demand. Testing more individuals with the same capacity leads to increases in the total cost and average utilization of testing centers. These results indicate that the solutions obtained with projected demand can satisfy the actual demand in a timely manner without creating significant variations from the anticipated resource utilizations and total cost.

We also test the model under random demand scenarios. We generate three different scenarios for each week using a normal distribution with a mean and standard deviation of the realized demand values over that week. We first solve the model using realized demand values and then fix the locations and timings of capacity expansions. Next, we solve the model under each random demand scenario. The total demand values for each scenario and corresponding results are presented in Table [2.2](#).

When the solution with the realized data is evaluated under random demand scenarios, all demand is served in a timely manner for the majority of the cases with a very small portion ($< 1\%$) of delayed demand, in particular, for the scenarios of the medium demand week. The differences in the average utilization of pop-ups and existing centers, and total cost are caused by the deviation of the realized demand from the randomly generated demand values and are not significant. These results demonstrate that the developed

Table 2.2: Model outputs under realized and random demand scenarios.

Demand set	Scenario	Total demand	Delayed appointments (%)	Avg utilization of pop-ups (%)	Avg utilization of existing centers (%)	Total cost(\$)
December (high)	Realized	13,933	0.0	80.9	71.3	864,513
	Random 1	13,968	0.0	81.1	71.2	864,524
	Random 2	13,901	0.0	81.4	69.4	862,825
	Random 3	13,980	0.0	81.7	71.2	866,753
April (medium)	Realized	9,508	0.0	76.3	58.5	583,731
	Random 1	9,774	0.1	76.3	58.7	583,733
	Random 2	9,338	0.0	76.8	56.8	573,759
	Random 3	9,532	0.3	76.7	61.7	599,358
August (low)	Realized	5,231	0.0	89.3	37.3	320,672
	Random 1	5,186	0.0	89.9	36.7	323,942
	Random 2	5,295	0.0	89.9	36.8	324,409
	Random 3	5,287	0.0	89.5	36.1	318,047

model leads to high-quality solutions, which are robust under demand uncertainty, for the case study.

2.5.2 Sensitivity Analysis

Input parameters including the number of candidate locations for pop-up centers, weights of delayed appointments and specimens in the objective function, available budget, length of the planning horizon, testing demand, and maximum travel distance may significantly affect the model outcomes. Hence, in this section, we present detailed sensitivity analyses to evaluate the effects of these parameters on the results.

We first assess the scalability of our model and solution potential with the commercial solver CPLEX on larger problem instances. Our base case problem instances with 26 candidate locations (i.e., FSAs) were solved to optimality by CPLEX in 41.8, 20.0, and 1.2 seconds for high, medium, and low demand weeks, respectively, using the default settings. We generated larger problem instances by doubling, tripling, and quadrupling the number

of candidate locations, i.e. 52, 78, and 104 candidate locations. Under the three demand scenarios (high, medium, and low) and three new problem sizes, we tested nine additional problem instances by setting a time limit of two hours to CPLEX. Two instances out of three demand scenarios with 52 candidate locations were solved to optimality in 21 and 405 seconds. We observed that CPLEX was able to produce very high-quality solutions within two hours of run time for the remaining problem instances achieving average optimality gaps of 0.05%, 0.40%, and 0.16% with 52, 78, and 104 node instances, respectively. Accordingly, for larger problem instances, our results show that decision-makers can employ off-the-shelf solvers with reasonable time limits to obtain good-quality solutions.

2.5.2.1 The Relative Importance of Delayed Appointments and Specimens

The model with the min-delay objective minimizes the weighted sum of delayed appointments and specimens. The decision-maker can assign relative weights to the delayed appointments and specimens based on their importance when using the current model. For the case study presented in Section 2.5, we assigned a higher weight to the delayed appointments since the laboratory capacity was not a limiting factor in Ontario as the delayed specimens are rerouted and processed at the labs with the available capacity within the provincial laboratory network. To assess the trade-off between the two objectives, we now test the model with different weight coefficients assigned to the delayed appointments (α) and specimens ($\beta = 1 - \alpha$). The results for various α values under high-, medium-, and low-demand scenarios are presented in Figure 2.9.

When the weight of delayed appointments is greater than that of delayed specimens

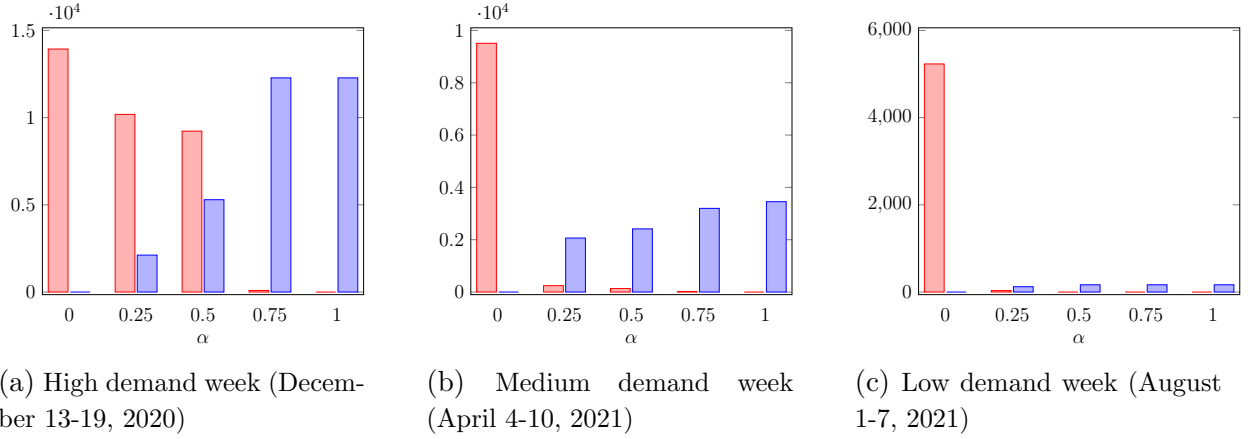


Figure 2.9: Number of delayed appointments (red) and delayed/rerouted specimens (blue) based on different weights in the objective function.

(i.e., when $\alpha > 0.5$), the model allocates most of the budget towards capacity expansion to test as many people as possible. As expected, when the objective weight of delayed appointments reaches zero, the model suggests testing nobody to minimize the number of delayed specimens. This confirms that assigning a weight of zero to delayed appointments would not yield meaningful results in practice. The marginal effect of increasing the weight α in reducing the number of delayed appointments is significant during the weeks with high demand; however, this marginal effect diminishes when demand decreases. The results of this analysis suggest that incorporating lab capacity as an additional decision variable may be desired for effectively managing high-demand scenarios, and can be a promising direction for future research.

2.5.2.2 Available Budget

The model with the min-cost objective finds the minimum total cost required to test everyone on time. We now conduct further analysis to evaluate the impact of budget on

the percentage of total demand receiving delayed appointments. We use the low demand week in August to perform the analysis. The results are presented in Table 2.3. The first column of Table 2.3 shows the available budget as a percentage of the minimum required budget to test everyone on time. The second column indicates the percentage of total demand receiving a delayed appointment. The third, fourth, fifth, and sixth columns specify the average number and utilization of pop-up testing centers opened, average capacity expansion, and utilization of the existing centers, respectively. Finally, the last column reports the solution time of the model.

The results in Table 2.3 demonstrate that at least one pop-up center should be opened in order not to have any delayed appointments. Even though existing testing centers are not fully utilized, a pop-up is required to test everyone due to the maximum travel distance requirement as there is no testing center within 20 km of several FSAs. Moreover, the delayed appointments gradually decrease to 6% at a similar rate as the budget increases up to 90% of the base case, beyond which the reduction in delayed appointments is quite limited. This indicates that, if feasible, 90% of the base case budget could be an ideal solution for reducing the delayed appointments cost-efficiently. When 90% of the minimum required budget is used, no pop-up center is opened, and existing centers could test 94% of the people on time.

2.5.2.3 The Value of the Multi-period Model

In this section, we analyze the potential benefits of using a multi-period model. We perform this analysis under four different planning horizons (i.e., one, two, three, and four weeks)

Table 2.3: Solutions for different values of the available budget using low demand week in August.

Available Budget (%)	Delayed appointments (%)	Avg # of opened pop-ups	Avg utilization of pop-ups	Avg utilization of pop-ups opened (%)	Avg capacity expansion for existing centers (%)	Avg utilization of existing centers (%)	Solution time (sec)
10	90	0	0	0	0	3.4	1.7
20	79	0	0	0	0	10.3	2.2
30	69	0	0	0	0	16.6	6.3
40	58	0	0	0	0	24.3	55.3
50	48	0	0	0	0	28.4	92.7
60	37	0	0	0	0	35	72
70	27	0	0	0	0	41.3	8.4
80	16	0	0	0	0	47.7	90.7
90	6	0	0	0	0	53.1	684.13
100 (Base case)	0	1	89.3	0	0	37.3	1.2

Table 2.4: Comparison of the performances of the multi-period and static models.

Instance number	Demand set	Planning horizon	Static model			Multi-period model			
			Testing cost (\$)	Capacity increase cost* (\$)	Solution time (sec)	Testing cost (\$)	Capacity increase cost* (\$)	Solution time (sec)	Capacity increase cost difference* (%)
1	December (high)	1-week	778,871	48,972	10	778,900	47,892	25.3	2.2
2		2-week	1,591,177	107,408	38.3	1,591,516	99,876	143.9	7.5
3		3-week	2,407,966	190,848	50.7	2,410,576	155,968	184.5	22.4
4		4-week	3,097,054	254,464	55.5	3,101,338	190,984	224.7	33.2
5	April (medium)	1-week	553,952	31,808	4.2	554,208	29,628	41.6	7.3
6		2-week	1,118,646	63,616	34.7	1,120,328	52,556	89.6	21
7		3-week	1,637,944	95,424	61.1	1,641,131	69,428	126.1	37.4
8		4-week	2,091,696	127,232	111.7	2,095,515	91,572	106.7	39
9	August (low)	1-week	304,776	15,904	1.1	304,776	15,904	1.5	0
10		2-week	626,260	31,808	1.3	626,260	31,808	1.3	0
11		3-week	956,066	48,384	2.2	956,091	47,744	1.6	1.3
12		4-week	1,293,080	63,616	3.4	1,293,080	63,616	2.5	0

*Capacity increase refers both to opening pop-up centers and expanding the capacity of existing ones.

with low, medium, and high-demand scenarios, which constitute a total of 12 instances. We first solve a static model assuming that the decisions of opening the pop-up testing centers and expanding the capacity of existing ones are made once at the beginning of the planning horizon and remain the same thereafter. We then solve the multi-period model by making the decisions of capacity increases at the beginning of each day as in our previous analyses. We compare the total costs of testing people, opening pop-up testing centers, and expanding the capacity of existing ones using static and multi-period models. The results are presented in Table 2.4 and Figure 2.10.

In most of the solutions presented in Table 2.4, the static and multi-period models incur similar testing costs, which constitute the majority of the total cost. This is because testing cost mainly depends on the number of people to be tested, which is the same in both models. The slight differences are due to the change in transportation costs that depend on the proximity of the specimen collection centers to the lab.

The total cost associated with the multi-period model is usually less than that of the static one as the former incurs significantly less costs for opening pop-ups and expanding the capacity of existing centers under high and medium demand scenarios. Observe from Figure 2.10 that the savings in the costs of capacity expansion and opening pop-ups with the multi-period model, compared to the static one, can be up to 39%. In more than half of the instances with high and medium demand scenarios, the associated cost savings are above 20%. For the instances with low demand scenarios, on the other hand, the savings in costs are insignificant. The multi-period model dynamically determines the locations and timings of the capacity expansions considering the fluctuation in the testing demand. Therefore, the new pop-up centers are opened and the capacities are expanded exactly when

they are needed throughout the planning horizon, rather than the more costly option of implementing all these changes at the beginning for the whole planning horizon as done by the static model.

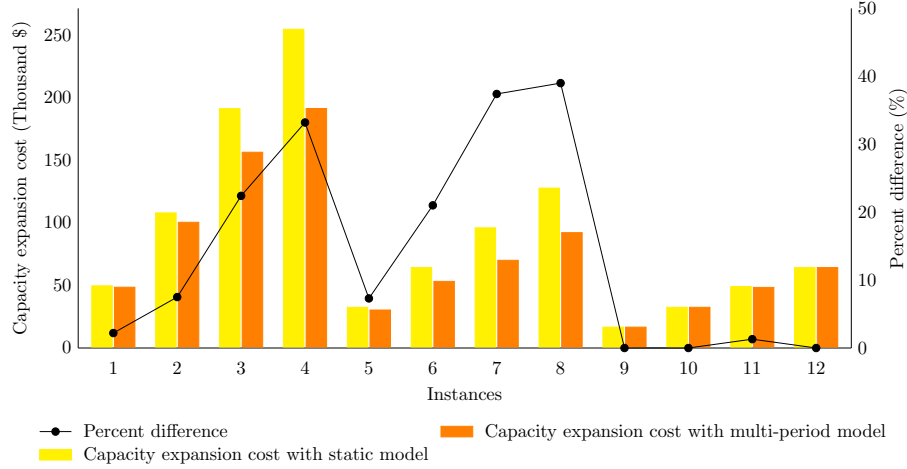


Figure 2.10: The value of multi-period model on different instances.

Our results show that there can be considerable savings in total costs of opening pop-up centers and capacity expansions by using the developed multi-period model. However, the multi-period model can be harder to implement in practice due to the need to frequently change decisions regarding the facilities. In this context, it is important to note that the differences between the costs of the multi-period and static models are not as much for the instances with a 1-week planning horizon (Table 2.4). The good performance of the static one-week policy should not be interpreted as limited room for improvement but as an opportunity. This result, which is possible to obtain thanks to the developed model, implies that making COVID-19 testing center location and capacity expansion decisions weekly can be more practical and equally cost-efficient compared to making these decisions on a day-by-day basis. On the other hand, public health decision-makers should avoid

implementing static decisions for more than one week as this may incur extra costs to the system.

2.5.2.4 Testing Demand and Maximum Travel Distance

We also test our model under different demand values and provide details of our results in Appendix A.1. We consider the low, medium, and high demand weeks from Section 2.5.1 as base cases and increase the corresponding demands by up to 50% with 10% increments. For the low demand week, compared to the base case, the model does not open additional pop-up testing centers until the demand is increased by 50%, i.e., the increase in testing demand can be served by using the base case pop-up center and expanding the capacity of the existing assessment centers. For medium and high demand weeks, the average number of opened pop-up testing centers increases with demand.

The maximum travel distance is taken as 20 km for the base case scenarios. Since this parameter affects the numbers and locations of pop-up testing centers, we additionally solve the model using different maximum travel distance values (will be referred to as L) for each demand scenario to capture its effect on the model output. Moreover, this distance could be lower for particular regions with limited parking space. Therefore, we test for $L \in \{5, 10, 15, 20, 25, 30\}$. When the maximum travel distance increases, more people can get access to testing from a particular existing or pop-up testing center. This results in the opening of fewer pop-up testing centers, as existing capacity can be better utilized to serve remote demand, as well as an increase in the average utilization of the opened pop-ups. On the other hand, when the maximum travel distance decreases, more pop-up testing centers

are needed which leads to lower utilization of some pop-up testing centers.

2.6 Managerial Implications

Our model and analyses provide practical plans and valuable insights for public health decision-makers to dynamically manage testing center capacity for COVID-19 in response to the evolving needs of the pandemic. The primary objective of the MOH is to ensure that the necessary capacity increases are made to test everybody on time with limited resources. Thus, the decision-makers must consider conflicting interests and balance the trade-off between total cost and total demand receiving delayed appointments. The formulation with a min-delay objective allows decision-makers to minimize the total demand receiving delayed appointments considering the capacity, and turnaround time limitations for a given budget. By setting the budget to the right level, the decision-makers can use the proposed model to minimize delayed appointments cost-effectively. This way, the proposed model can be used to meet the requirements of all stakeholders and balance their competing interests by efficiently using the available resources.

It is essential to consider the travel distance of people tested, which is an indicator of accessibility to COVID-19 testing. Our model addresses this by incorporating a maximum travel distance and ensuring that everyone has access to a testing center within a specified range. The maximum travel distance (MTD) depends on various factors, including the demographical and spatial features of the considered region. For instance, a longer MTD may be suitable in rural areas, while a shorter MTD may serve better in metropolitan areas. Our model captures the effect of traveling distance on the utilization of testing

capacity and use capacity extension decision to promote accessibility to COVID-19 testing services. Therefore, public health decision-makers can also utilize the proposed model as a tool to design a more accessible COVID-19 testing network under various MTD scenarios.

Our results show that as the COVID-19 load in the population increases, it is optimal to place the majority of the testing load on pop-up centers and utilize existing centers to cover incremental demand increases between the openings of pop-up centers. This is mainly because pop-up centers have lower unit costs of increasing testing capacity and provide locational flexibility. This implies that public health decision-makers may rely on opening pop-up centers to increase their specimen collection capacity as their primary response to increasing demand for testing, while increasing existing testing center capacities may be a secondary option to avoid the lump sum costs. Pop-up testing centers should be particularly considered in densely populated FSAs with limited nearby existing testing centers.

Our results further imply that while developing a testing capacity expansion plan (either as an emergency response strategy before a new pandemic or planning during a new one), decision-makers can identify a predetermined set of locations for pop-up centers using the proposed model. Subsequently, a subset of these locations can be opened in a particular order based on the fluctuations in demand to cover various demand increase scenarios (e.g., a steady increase in infection load due to infection spread or a much faster one due to an emerging virus variant). Moreover, when selecting the locations of pop-up centers or determining the capacity expansion of existing centers, their proximity to the labs should be considered to minimize the transportation costs of specimens.

Lastly, it is important to consider the frequency of capacity expansion decisions in terms of both cost and practicality. The dynamic nature of the proposed model requires making decisions regarding testing center locations and capacity expansions on a day-by-day basis. This level of adaptability may pose challenges in terms of logistics, coordination, and resource management. By adopting an appropriate frequency of decision-making approach, decision-makers can find a balance between cost-efficiency and practicality. Our analysis suggests that weekly decisions can be practical and equally cost-efficient compared to daily decisions.

2.7 Conclusions

In this chapter, we study a facility location and capacity allocation problem for COVID-19 testing motivated by the public health system in Ontario, Canada. We develop a mathematical model to determine the optimal timing and locations of pop-up testing centers, capacity expansions for the existing centers, assignment of demand regions to centers, and the assignment of specimens to the labs under budget, capacity, and turnaround time constraints. We propose two different objective functions that can be used based on the needs of the healthcare system and the perspectives of the public health decision-makers. The first objective is to minimize the weighted sum of delayed appointments and specimens, while the second objective is to minimize the total cost under a given acceptable value of delayed appointments and specimens.

We implement the developed model in a case study from the Region of Waterloo public health unit using real data and conduct several numerical experiments. The results of our

analysis provide insights into optimal locations and capacities of testing centers, the timing of capacity expansions, and the benefit of improving testing performance in Ontario. In our results, opening pop-up centers is preferred over capacity expansion due to their flexible locations and lower unit costs of testing. In the optimal solutions, pop-up centers cover the major load when testing demand is high, but existing centers are preferred to cover incremental increases between two pop-up openings. We observe that there is a preferred set of pop-up locations in the optimal solutions and the model generally opens a subset of those locations with the changes in demand. The model strategically locates pop-ups or expands the capacity of existing centers around the lab to reduce transportation costs. Moreover, pop-ups tend to be located in densely populated FSAs with limited existing centers.

Our numerical experiments with retrospective data help identify the bottlenecks in COVID-19 testing and provide strategies and insights to overcome them. In addition, we show that the developed model can be combined with prediction methods and used as a decision-aid tool for proactively determining the need for capacity increases based on the estimated new COVID-19 cases. Such a decision aid tool can be quite useful for public health decision-makers to design effective and dynamic COVID-19 testing strategies against new COVID-19 variants (e.g., Omicron, Delta, BA.5). The results of our analysis with uncertain demand indicate that the developed model provides robust solutions when actual demand shifts from the predicted values. Our analysis shows that there can be high-cost savings by using the proposed multi-period model as compared with a static counterpart.

While the focus of our study is COVID-19, testing plays a significant role in the control

of other infectious diseases and the developed model can be applied to those as well. Based on the reported outbreaks in recent years, the frequency of infectious disease outbreaks is expected to increase in the future ([Houlihan and Whitworth 2019](#)). Since these outbreaks are inevitable, proactive actions to improve our readiness should be studied now. In this context, the model can be used or extended to develop response plans for future infectious disease outbreaks (e.g., monkeypox), especially for those that use PCR tests with a similar diagnostic process (i.e., specimen collection plus laboratory analysis) ([Yang and Rothman 2004](#), [Adler et al. 2022](#)). In case of a future pandemic, the developed model may help control the spread of the disease at the early stages of the pandemic by proactively managing testing capacity to avoid the challenges and difficulties we have had since the beginning of the COVID-19 pandemic.

The developed model can be extended in several directions. First, since lab capacity is not binding in our study, we do not include the decisions regarding the capacity expansions for the labs. A natural extension could be to allow for the capacity expansions of the labs as well. We obtain the optimal results for our case study using a commercially available solver in very reasonable times, hence, we did not develop any specialized algorithms. In future research, decomposition methodologies, heuristic and metaheuristic algorithms can be developed and employed to effectively solve large-sized instances of the problem.

Chapter 3

Optimizing Surveillance Protocols for Hospital-Acquired Infections: Case of MRSA

3.1 Introduction

Nosocomial or healthcare-associated infections (HAIs) acquired within healthcare facilities cause a significant burden on healthcare systems due to the associated morbidity, mortality, prolonged hospital stays , and substantial financial burdens ([Haque et al. 2018](#), [Johnstone et al. 2019](#)). In the US, HAIs affect approximately 1.7 million individuals annually, i.e., 1 in every 31 hospital patients and 1 in every 43 nursing home residents acquire HAI, with associated costs ranging from \$28 and \$45 billion per year ([Haque et al. 2018](#), [CDC 2022](#)).

Canada faces a similar toll with 5,400 HAI-associated deaths in 2018 and costs amounting to \$1.4 billion (PHO 2023). HAIs caused by antimicrobial-resistant organisms (AROs), which are especially concerning given their complex treatment process, are on the rise in many healthcare settings (Johnstone et al. 2019). Infection prevention and control (IPAC) efforts including hand hygiene, contact precautions, and testing effectively reduce HAI and ARO transmission in hospitals (Johnstone et al. 2019). Among AROs, Methicillin-Resistant *Staphylococcus aureus* (MRSA) stands out as a leading cause of HAIs with severe complications (Samia et al. 2022). Despite infection control measures, MRSA prevalence has been increasing after the COVID-19 pandemic, e.g., by 7.6% between 2019 and 2021, underscoring the ongoing importance of effective MRSA surveillance and management in hospitals (CDC 2022).

IPAC guidelines recommend surveillance testing and additional precautions to mitigate nosocomial MRSA transmission (Johnstone et al. 2019, Bächli et al. 2022). Public Health Ontario reports that all Ontario hospitals have active universal and/or targeted (for high-risk individuals) MRSA surveillance programs. Roommates of new nosocomial MRSA cases have high risk for MRSA acquisition, and thus, are isolated and tested in approximately 76% of Ontario hospitals (PHO 2023). Ontario’s Provincial Infectious Disease Advisory Committee (PIDAC) recommends that such individuals should undergo multiple surveillance tests, with one occurring at least seven days after the last exposure (PIDAC 2013). Following the detection of a new MRSA case in a shared room, the index case is removed, and roommates are generally isolated while awaiting the results of surveillance testing, usually using conventional cultures (i.e. chromogenic media).

A few controversies around optimal MRSA surveillance testing include the laboratory

modality and timing of specimen analysis. MRSA colonization detection by any technique relies on the quantity of organisms to be above the test’s detection threshold (at that body site) at the time of assessment. Therefore, the performance of surveillance testing may differ over time (i.e. post exposure) and the patient must reach a certain organism burden to be truly detected ([PIDAC 2013](#)). While most guidelines recommend culture tests for following up with exposed roommates, some studies promote PCR tests for their comparable accuracy and faster turnaround times ([PIDAC 2013](#), [Baby et al. 2017](#), [Turner et al. 2021](#)). Given that isolation duration (and its associated costs) and future risk of transmission (while in the facility) are influenced by the laboratory result, understanding the optimal testing method and timing is critical to optimize IPAC measures. However, the uncertain time to being above a detection threshold for MRSA colonization complicates the decision-making process regarding the timing of post-exposure testing. Testing shortly after exposure may result in lower sensitivity and a higher rate of false negatives leading to missed MRSA cases and future transmissions ([Evison and Mühlemann 2008](#)). On the other hand, unnecessary isolation presents challenges for both hospitals (bed management, costs) and patients (increased psychological distress) ([Tran et al. 2017](#), [Turner et al. 2021](#)). Additionally, extended isolation increases the exposure of non-colonized roommates to other undetected MRSA cases from the initial exposure. Therefore, reducing unnecessary isolation without increasing missed cases is desirable.

Although the timing of MRSA testing is important for the surveillance of exposed roommates, existing guidelines do not specify the optimal timing of roommate post-exposure testing or the test modality (culture vs. PCR test). There are a few studies analyzing different MRSA testing strategies. For example, [Ng et al. \(2012\)](#) demonstrated that the

sensitivity of PCR testing on day 3 was comparable to that of culture testing on day 6. Building on these findings, [Lin et al. \(2023\)](#) evaluated the performance of two MRSA surveillance methods, conventional culture on day 6, and direct PCR on day 3, employing simulation. They showed that switching to PCR testing resulting in a shorter isolation duration not only reduces costs but also improves health outcomes. However, these studies only compare a few periodic strategies, specifying the timing of MRSA tests regardless of the number and compositions of the ward rooms under isolation.

Given the computational challenges of comparing all dynamic MRSA testing protocols using a simulation model, analytical models are needed to determine the optimal timing of PCR tests as well as the interval of repeated sampling for the roommates of index MRSA cases. Although several completely and partially observable Markov decision process (POMDP) models have been proposed to address similar challenges for chronic diseases, there are very few analytical models for infectious diseases that consider randomness, incomplete test information, and the composition of populations under isolation. To the best of our knowledge, no such model exists for in-hospital infections.

In this context, we develop a novel finite-horizon discrete-time Markov decision process (MDP) model to determine the optimal MRSA surveillance testing and isolation decisions for the exposed roommates. We separately consider minimizing the total expected loss of quality-adjusted life years (QALYs) to represent the patient perspective and minimizing the expected number of MRSA colonizations to represent the clinical perspective. Optimal testing problems under stochastic disease progression are often modeled as POMDPs due to imperfect test information. However, POMDPs are computationally intractable for problems with large state spaces, especially those for infectious diseases that require track-

ing the entire susceptible population. The novelty of our approach lies in developing an efficient MDP formulation that is equivalent to a POMDP under reasonable assumptions related to the bounds on the number of MRSA tests, isolation duration, and the size of the susceptible population. This formulation enables us to solve the problem optimally.

3.2 Literature Review

The effectiveness of MRSA testing has been extensively studied with a focus on universal (testing all patients) or targeted (testing patients with significant risk factors) admission screening, i.e., testing incoming patients for MRSA upon their admission to hospitals. Universal screening, while effective in identifying a broad spectrum of carriers, may pose challenges due to its associated costs and resource consumption ([Roth et al. 2016b](#)). On the other hand, targeted screening of patients with risk factors, such as a recent history of having MRSA, hospitalization or residence in long-term care facilities, limits unnecessary testing and reduces resource consumption ([Deeny et al. 2013](#)). Numerous studies have compared the (cost-)effectiveness of universal and targeted MRSA screening strategies using simulation models, decision trees, and retrospective data analyses according to the number of MRSA transmissions and infections, total costs, and other patient outcomes ([Leonhardt et al. 2011](#), [Hubben et al. 2011](#), [Deeny et al. 2013](#), [Roth et al. 2016a,b](#)). Although the ongoing discussion regarding universal versus targeted screening remains controversial as results vary based on population characteristics, healthcare settings, and the prevalence of MRSA ([Roth et al. 2016b](#)), targeted screening is often found to be more cost-effective ([Leonhardt et al. 2011](#), [Roth et al. 2016a,b](#)). Recognizing the significant effect of pro-

longed exposure to an MRSA-positive case on the MRSA acquisition rate, [Bächli et al. \(2022\)](#) proposed and evaluated the MRSA contact screening strategy in a low-prevalence setting through a retrospective analysis. Their results suggested that targeted screening of exposed individuals in specific areas might be more effective than whole-ward (universal) screening in low-prevalence settings. Similar to [Bächli et al. \(2022\)](#), several studies focused on the surveillance of patients at higher risk of MRSA acquisition including the roommates of the primary MRSA cases identified by a positive MRSA test during an in-patient stay ([Moore et al. 2008](#)). Unlike admission testing, MRSA surveillance strategies for these patients need to specify the timing of the initial and follow-up tests as well as the conditions for terminating isolation based on test results. Some retrospective studies, such as [Moore et al. \(2008\)](#) and [Williams et al. \(2017\)](#), explored the acquisition rate of MRSA among roommates under existing surveillance or infection control/prevention practices to quantify the risks and associated factors. [Evison and Mühlemann \(2008\)](#) explored the effectiveness of MRSA surveillance testing in roommates shortly after exposure to an MRSA carrier following a double screening strategy, which involved conducting a second culture test four days after an initial negative culture test result. Their findings highlighted an incubation period for MRSA colonization, indicating that tests conducted immediately after exposure might not be sufficient to identify all carriers accurately. Later, [Ng et al. \(2012\)](#) studied the effectiveness of various culture- and PCR-based surveillance approaches for detecting MRSA conversion in roommates of MRSA index cases, using a retrospective data analysis. Their findings emphasized that PCR testing on the third day performs similarly to the culture test on the seventh day, in terms of the number of colonization detected. This suggests that PCR testing could shorten the duration of isolation by accel-

erating MRSA detection. Based on this insight, [Lin et al. \(2023\)](#) compared the efficiency of some conventional culture and direct PCR testing strategies among roommates of MRSA-positive patients in Canadian community hospitals using a simulation model considering various performance measures. Their findings indicated that switching to PCR testing with a shorter isolation duration not only reduces costs but also improves health outcomes by limiting the exposure of healthy roommates with unrecognized MRSA-positive cases. Moreover, unlike some previous studies, their research highlighted the importance of day 0 testing for the effectiveness of MRSA surveillance among the roommates of an index MRSA case.

Unlike admission screening, the literature on MRSA control and management among exposed roommates of MRSA-positive patients is notably scarce, leaving a critical gap in our understanding of effective surveillance practices in this population. Existing studies compared only a few selected surveillance strategies using simulation or statistical analyses, which lack the power to analyze all possible strategies to find the optimal one or conduct detailed multi-way parameter analyses to identify for which input parameter combinations alternative protocols may replace existing guidelines. Our work is the first attempt to fill this gap by proposing an analytical model that can identify the optimal protocols and provide comprehensive insights for policymakers on how they can improve MRSA surveillance practices by employing different testing modalities and partially dynamic testing strategies, evaluated according to relevant performance metrics, such as MRSA colonization, loss of quality-adjusted life years and total costs. To the best of our knowledge, this is the first analytical model focusing on MRSA surveillance among exposed roommates.

There is an extensive body of literature on operations research (OR) applications for

managing infectious diseases. These models either focus on capturing the disease dynamics in detail using advanced simulation models, or more general analytical models, primarily deterministic, to optimize decisions around testing, social distancing, and vaccination services as well as the location and resource allocation of these services. Most OR studies in this literature use epidemiological compartmental models (e.g., SIR (Susceptible-Infected-Recovered)), agent-based or discrete-event simulations, and linear or non-linear mixed integer programming models to track the number of patients at different disease stages and future disease propagation ([Barnes et al. 2010](#), [Akgun et al. 2023](#), [Abdin et al. 2023](#)). These studies have been reviewed in detail by several literature reviews ([Long and Brandeau 2009](#), [Rais and Viana 2011](#), [Silal 2021](#)). Most OR applications in this domain are either deterministic (ignoring stochastic disease propagation or test results) or employ simulation models, thus unable to determine the optimal strategy. The most relevant studies in this literature to ours are two agent-based simulation models developed to explore the transmission dynamics of MRSA in hospitals and ICU departments and the effectiveness of various infection control practices including hand hygiene, testing, decolonization and isolation ([Barnes et al. 2010, 2020](#)). These models primarily aim to facilitate early detection and treatment of primary carriers, rather than focusing on exposed roommates. The first study considered disease spread within the hospital and the broad list of infection control interventions listed above ([Barnes et al. 2010](#)). The second study focused on ICU settings where patient-to-patient transmission is unlikely and thus not considered. [Barnes et al. \(2020\)](#) utilized their agent-based simulation to train prediction models specifying high-risk individuals and compared the effectiveness of these models in implementing contact precautions.

Finally, several MDP and POMDP models have been proposed to capture disease progression and optimize disease testing, screening, or surveillance decisions for various conditions such as cancer, organ failure, and diabetes. As reviewed in earlier studies ([Alagoz et al. 2010](#), [Rais and Viana 2011](#), [Steimle and Denton 2017](#)), the vast majority of these MDP/POMDP models focus on chronic diseases, where each individual’s disease progression is independent and can be modeled separately. On the other hand, modeling an infectious disease requires tracking the changes in the number of infected individuals in the population. Only a few MDP models addressed infectious disease propagation, particularly in the context of epidemic control for human or animal populations ([Yaesoubi and Cohen 2011a,b](#), [Viet et al. 2012](#), [Codella 2014](#), [Viet et al. 2018](#), [Song et al. 2024](#)). These studies often consider a closed population and a state space composed of compartments from classical models such as SIR or SEIR (Susceptible-Exposed-Infected-Recovered) models. They apply different methodologies including state aggregation and approximate dynamic programming to solve their problems for large instances. Using these models, they analyzed the optimal intervention strategies (e.g., vaccination, transmission-reducing measures, and pharmaceutical interventions) under resource constraints. [Song et al. \(2024\)](#) extended their MDP-based epidemic control model into a distributionally robust MDP (DRMDP) to address uncertainty in transition probabilities. All of these studies assume that the number of patients in each compartment is completely observable and do not consider disease testing as an action. Among the above studies, [Codella \(2014\)](#) is particularly relevant. [Codella \(2014\)](#) proposed an infinite-horizon constrained continuous-time MDP model to determine the optimal infection control practices for a different in-hospital infection; *Clostridium difficile* (*C. difficile*), aiming to minimize the total expected health

disutility of patients in a hospital. Like others, this model considered states representing the number of susceptible, colonized, and infected patients in the hospital, without considering room settings, thereby limiting the pathways for disease spread. They considered four possible control strategies, excluding disease testing, and assumed that all states are completely observable. Finally, [Singh et al. \(2020\)](#) proposed a POMDP model for the sequential testing of infectious diseases such as COVID-19 to minimize the number of infected individuals. Their model optimally decides whom to test within a fixed population. Although they considered testing and quarantine decisions of individuals incorporating social contact graphs; they assumed that tests are perfect, i.e., accuracy is 100% ignoring the possibility of false negatives. Unlike the discussed MDP and POMDP models above, we consider sequential/dynamic disease testing and isolation decisions together, assuming partially observable health states and imperfect test results.

To the best of our knowledge, no study has employed an MDP/ POMDP model to determine the optimal dynamic testing protocol for infectious diseases in a healthcare facility, specifically incorporating room settings, time-dependent test sensitivities and new index case detections. To address this gap in the literature, we propose an MDP model that efficiently tracks the changes in the composition of isolated rooms, providing sufficient statistics to calculate the probability distribution of true health states for each remaining patient in the room. Our novel state-space representation, despite requiring tedious calculations, allows us to model the MRSA surveillance problem as a discrete-time MDP rather than a POMDP and solve it efficiently for realistic instances. Thus, we introduce a new alternative approach to tackle similar infection control problems within healthcare settings.

3.3 MDP Formulation

We present an MDP model that determines the optimal testing decisions for the exposed roommates of an index MRSA case given the number and composition of isolated rooms. The MDP model tracks the number of exposed roommates in the same room and the number of days they spent together before each test. Using Bayesian inference, the MDP model keeps track of the probability distribution of potential transmission in the hospital, whereas disease transmission dynamics in each room are captured with a Hidden Markov Model (HMM). Table 3.1 lists the notation used in this work.

3.3.1 Markov Disease Model

Roommates stay in the same room with the index MRSA case until s/he is diagnosed and removed. Upon detecting the index case, all exposed roommates are placed into contact isolation and undergo follow-up tests. Each exposed roommate may acquire the disease due to pre-isolation (primary) transmission with a probability equal to the prevalence of MRSA colonization on day 0 (ρ). During the isolation, colonized roommates from the pre-isolation period may spread MRSA to noncolonized roommates (secondary transmissions) with probability $\underline{p}$.

We define the MRSA stages of the exposed roommates as noncolonized, colonized undetectable, and colonized detectable. The colonized detectable/undetectable stage represents the patients colonized with MRSA who can or cannot be identified by MRSA tests, respectively. Note that the test has imperfect accuracy and works with a certain probability.

Table 3.1: Model Notation.

Notation	Description
State Variables and Indices	
$i \in \mathbf{I} = \{1, \dots, \delta\}$	The index for PCR tests administered, where δ is the maximum number of tests
$j \in \mathbf{J} = \{1, \dots, \omega\}$	The index of isolated rooms, where ω is the maximum number of rooms
$\gamma_j \in \mathbf{M} = \{1, \dots, M\}$	The type of room $j \in \mathbf{J}$
$n_i^j \in \mathbf{H} = \{0, \dots, H^{\gamma_j}\}$	The number of exposed roommates in room j before the i^{th} PCR test, where H^{γ_j} is the room size for γ_j
$t_i^j \in \Theta = \{0, \dots, N\}$	The number of days exposed roommates in room $j \in \mathbf{J}$ spend together in isolation before the i^{th} PCR test, where N is the maximum isolation duration
$t \in \mathbf{T} = \{0, \dots, T\}$	The decision epochs of the MDP model, e.g., current day of the year
$n \in \mathbf{N} = \{0, \dots, N\}$	The period for Markov Chain, i.e., the day of the isolation
$\lambda_t \in \mathbf{\Lambda} = (\lambda_r, \lambda_1, \dots, \lambda_\psi)$	The rate of recognizing a new index MRSA case, where ψ represents the number of risk groups and λ_r represents the regular rate
$\mathbf{q}_i^j = \begin{bmatrix} n_i^j \\ t_i^j \end{bmatrix}$	The vector indicating that n_i^j roommates spent t_i^j days together in isolation before the i^{th} PCR test, $\forall t_i^j \in \Theta, n_i^j \in \mathbf{N}$
$\mathbf{Q}^j = (\mathbf{q}_1^j, \dots, \mathbf{q}_\delta^j) \in \mathbb{N}_0^{2 \times \delta}$	The matrix representing the collection of vectors $\mathbf{q}_i^j$ for room $j, \forall i \in \mathbf{I}, j \in \mathbf{J}$
Model Components and Parameters	
ρ	MRSA colonization prevalence at the beginning of isolation
$\underline{p}$	MRSA transmission probability from a colonized to noncolonized patient
$\bar{p}$	MRSA transmission probability to a noncolonized patient during isolation
d_0	The probability of detecting a colonized patient on post-exposure day 0
q	The daily transition probability from undetectable to detectable during isolation
p_{γ_j}	The probability of having a room type $\gamma_j \in \mathbf{M}$
α, β	Sensitivity and specificity of the PCR test
T^+, F^-	True positive and false negative
$X_n^j = (h_0, h_1, h_2) \in \Omega^{\gamma_j}$	The state of the HMM representing the number of noncolonized (h_0), undetectable colonized (h_1), and detectable colonized (h_2) exposed roommates in room $j \in \mathbf{J}$ on day $n \in \mathbf{N}$, where $\Omega^{\gamma_j} = \{(h_0, h_1, h_2) \in \mathbb{N}_0^3 \mid (h_0 + h_1 + h_2) \leq H^{\gamma_j}\}$
$\mathbf{s}_t = (\mathbf{Q}_t^1, \dots, \mathbf{Q}_t^\omega, \lambda_t) \in \mathbf{S}$	The state of the MDP representing room compositions in isolation and rate of recognizing an index MRSA case, where $\mathbf{S} \equiv \mathbf{Q}^1 \times \mathbf{Q}^2 \times \dots \times \mathbf{Q}^\omega \times \mathbf{\Lambda}$
$a_t^j \in \mathbf{A}^j(\mathbf{Q}_t^j) \subset \mathbf{A}$	The action for room $j \in \mathbf{J}$, where $\mathbf{A} = \{\text{NT, TDR, TR}\}$
$\mathbf{a}_t = (a_t^1, a_t^2, \dots, a_t^\omega) \in \mathbf{A}_t$	The action for isolated rooms, where $\mathbf{A}_t \equiv \mathbf{A}^1(\mathbf{Q}_t^1) \times \dots \times \mathbf{A}^\omega(\mathbf{Q}_t^\omega)$
$P(\mathbf{s}_{t+1} \mathbf{s}_t, \mathbf{a}_t)$	The transition probability function, $\forall \mathbf{s}_t, \mathbf{s}_{t+1} \in \mathbf{S}, \mathbf{a}_t \in \mathbf{A}_t$
V_t^*	Optimal value function for the expected loss of QALYs at time t
Y_t^*	Optimal value function for the expected MRSA colonizations at time t
$\nu \in [0, 1]$	The discount factor
$d_{col}, d_{iso}, d_{inf}$	Disutility of MRSA decolonization, isolation, and MRSA infection
$c_{col}, c_{iso}, c_{PCR}, c_{cul}$	Cost of MRSA decolonization, isolation (per day), and PCR and culture tests
$d^j(\mathbf{Q}_t^j, a_t^j)$	The expected disutility incurred for room $j \in \mathbf{J}$ if action a^j is taken
$r^j(\mathbf{Q}_t^j, a_t^j)$	The expected number of MRSA colonizations for room $j \in \mathbf{J}$ if action a^j is taken
$c^j(\mathbf{Q}_t^j, a_t^j)$	The expected cost incurred for room $j \in \mathbf{J}$ if action a^j is taken
$z^j(\mathbf{Q}_t^j, a_t^j)$	The expected number of missed cases in room $j \in \mathbf{J}$ if action a^j is taken
$f^j(\mathbf{Q}_t^j, a_t^j)$	The expected number of false positives in room $j \in \mathbf{J}$ if action a^j is taken

In reality, both PCR and culture test sensitivities depend on the testing time (Ng et al. 2012), as the bacterial load changes during the incubation period. However, specific test sensitivities for each day are not readily available in the literature, and limited data is available to estimate them accurately. To address this, we defined two separate stages for colonized patients: detectable and undetectable. Instead of using time-varying sensitivities, we assume a constant test sensitivity and introduce the concept of stochastic transition from undetectable to detectable stage to capture the effect of the latency period on test sensitivity. This approach aligns with clinical knowledge of the disease progression and enables us to represent a range of time-variant test sensitivities with two constant model parameters. Specifically, we consider a time-stationary test sensitivity and a daily transition probability from undetectable to detectable MRSA colonization stage, effectively incorporating time-varying test sensitivities. It is important to note that another potential health state is infection. However, our data source indicates that MRSA infection is very rare in Canadian hospitals, especially in Ontario, which is the focus of our study. As a result, we assume the likelihood of MRSA infection during isolation is zero and only consider transitions among noncolonized, colonized undetectable, and colonized detectable stages. The model can be extended to include infection if necessary.

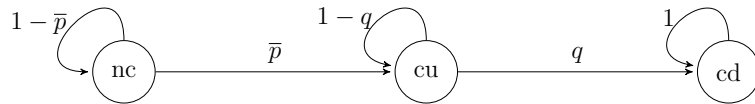


Figure 3.1: Transmission and progression dynamics for a patient in a cohort room. In the figure, nc , cu and cd represent the non-colonized, colonized undetectable and colonized detectable states, respectively, $\bar{p}$ denotes the probability of developing MRSA colonization, and q refers to the probability of becoming detectable.

We model the disease progression of MRSA in roommates using the Markovian model state transition scheme illustrated in Figure 3.1 for each patient. The figure highlights the transitions between the states and the associated probabilities. In a semi-private room, an exposed patient may develop colonization through contact with the index MRSA case before isolation, and progress through colonized states during the isolation. However, this patient cannot transmit the disease to anyone. On the other hand, in a cohort room, colonized patients can transmit the disease to noncolonized roommates in the same room during the isolation. Transmission probability, $\bar{p}$, depends on the number of colonized cases in the room. More specifically:

$$\bar{p} = 1 - (1 - \underline{p})^{h_1 + h_2} \quad (3.1)$$

where $\underline{p}$ is the transmission probability from a colonized to a noncolonized patient and $h_1 + h_2$ represents the total number of colonized cases in the room. When patients are first colonized with MRSA, they are in an undetectable colonization stage due to the insufficient incubation period and may transition from the undetectable to the detectable stage with a progression probability, q , during later days of isolation.

3.3.2 Hidden Markov Model

We model the MRSA transmission and progression among the roommates in a specific isolated room under a particular testing protocol as a discrete-time discrete-state hidden Markov model (HMM). $X_n^j = (h_0, h_1, h_2)$ denotes the hidden state of the HMM, where h_0 , h_1 , and h_2 represent the number of noncolonized, colonized undetectable, and colonized

detectable cases in room $j \in \mathbf{J}$ on day n , respectively. The state space of the HMM is defined as $\Omega^{\gamma_j} = \{(h_0, h_1, h_2) \in \mathbb{N}_0^3 \mid (h_0 + h_1 + h_2) \leq H^{\gamma_j}\}$. The initial state probability distribution, denoted by $\pi_{\mathbf{h}} \in \Pi$, represents the probability of being in state $\mathbf{h} = (h_0, h_1, h_2)$ on post-exposure day 0. This distribution follows a multinomial distribution specifying the number of noncolonized, colonized undetectable, and colonized detectable cases based on colonization prevalence (ρ) and detectability (d_0) on post-exposure day 0 as given in Equation 3.2.

$$\pi_{\mathbf{h}=(h_0,h_1,h_2)} = \frac{H^{\gamma_j}!}{h_0!h_1!h_2!} (1-\rho)^{h_0} ((1-d_0)\rho)^{h_1} (d_0\rho)^{h_2} \quad \forall \mathbf{h} \in \Omega^{\gamma_j} \quad (3.2)$$

The probability of being in state $\mathbf{h}'$ on day n , i.e., $P(X_n^j = \mathbf{h}')$, can be computed using the law of total probability. The formula integrates over all possible initial states, utilizing the initial state probabilities (Π) and the n -step transition probabilities as follows:

$$P(X_n^j = \mathbf{h}') = \sum_{\mathbf{h} \in \Omega^{\gamma_j}} \pi_{\mathbf{h}} P_{\mathbf{h}, \mathbf{h}'}^n \quad \forall \mathbf{h} \in \Omega^{\gamma_j} \quad (3.3)$$

where $\mathbf{h} = (h_0, h_1, h_2)$ and $\mathbf{h}' = (h'_0, h'_1, h'_2)$ denote the state vectors and the matrix $P_{\mathbf{h}, \mathbf{h}'}$ represents the n -step transition probabilities between states.

The observations are the test results and observation (emission) probabilities are determined based on the test results. Exposed roommates in the colonized-detectable stage can be identified as true positives with a probability equal to the test sensitivity (α) while colonized undetectable cases cannot be detected at all. Noncolonized roommates are identified as true negatives with a probability equal to the test specificity (β). True positives

will be removed from isolation for treatment, while false positives and test negatives will remain in isolation. Let o_n denote the observation on day n and O_k represent the event that k people are tested as MRSA positive including both true and false positives. The probability of O_k occurring, given the current state, is as follows:

$$P(o_n = O_k | X_n^j = \mathbf{h}) = \quad (3.4)$$

$$\sum_{l=0, l \leq k}^k \binom{h_0}{l} (1 - \beta)^l \beta^{(h_0-l)} \times \binom{h_2}{k-l} \alpha^{(k-l)} (1 - \alpha)^{h_2-(k-l)} \quad \forall k \leq h_0 + h_2$$

$$P(o_n = O_k) = \sum_{\mathbf{h} \in \Omega^{\gamma_j}} P(o_n = O_k | X_n^j = \mathbf{h}) P(X_n^j = \mathbf{h}) \quad (3.5)$$

Given k people are tested positive, the probabilities that ℓ of them are true positives and that among the $\sum_{i=1}^3 h_i - k$ negatives in the room, m of them are false negatives (missed cases) are given in Equations 3.6 and 3.7, respectively.

$$\frac{P(T^+ = \ell | o_n = O_k) = \sum_{\mathbf{h} \in \Omega^{\gamma_j}} \binom{h_0}{k-\ell} (1 - \beta)^{k-\ell} \beta^{(h_0-(k-\ell))} \times \binom{h_2}{\ell} \alpha^{\ell} (1 - \alpha)^{h_2-\ell} P(X_n^j = \mathbf{h})}{P(o_n = O_k)} \quad \forall \ell \leq k \quad (3.6)$$

$$\frac{P(F^- = m | o_n = O_k) = \sum_{\mathbf{h} \in \Omega^{\gamma_j}} \binom{h_2}{m-h_1} \alpha^{h_1+h_2-m} (1 - \alpha)^{m-h_1} \times \binom{h_0}{k-\ell} (1 - \beta)^{k-\ell} \beta^{h_0+\ell-k} P(X_n^j = \mathbf{h})}{P(o_n = O_k)} \quad \forall m \leq \sum_{i=1}^3 h_i - k \quad (3.7)$$

Next, we need to define the one-step transition probabilities for the HMM based on the transmission and progression model for a single patient to derive $P_{\mathbf{h}, \mathbf{h}'}^n$ in Equation 3.3. On

a day when no test is performed, the probability of observing no outcome ($o_n = \emptyset$) is 1. During no-test day, a certain number of roommates become colonized and some colonized undetectable patients transition into the detectable phase with a certain probability as defined in Equation 3.8. There is no transition between certain states and the resulting probability is 0.

$$P(X_{n+1}^j = \mathbf{h} - (c, d - c, -d) | X_n^j = \mathbf{h}) = \begin{cases} \binom{h_0}{c} \bar{p}^c (1 - \bar{p})^{(h_0 - c)} \binom{h_1}{d} q^d (1 - q)^{(h_1 - d)} & \forall c \leq h_0, d \leq h_1 \\ 0, & \text{otherwise} \end{cases} \quad (3.8)$$

On a test day, the transition probabilities are affected by the test outcomes. When exposed roommates are tested on day n during isolation, the probability of transitioning to a particular state after a very short period, ϵ , is updated based on the test results using Bayesian inference, as shown in Equation 3.9. Following this initial update, transitions between different colonization states occur with specific probabilities, similar to the process on no-test days. In particular, transitions from the noncolonized state to the undetectable colonized state, and from the undetectable colonized state to the detectable colonized state, occur via an intermediate state after the initial update, as described by Equation 3.10. This approach effectively captures state changes considering test results and natural disease progression.

$$P(\ddot{X}_{n+\epsilon}^j = \mathbf{h}' \mid X_n^j = \mathbf{h}, o_n = O_k) =$$

$$\frac{\binom{h_0}{h_0-h'_0}(1-\beta)^{h_0-h'_0}\beta^{h'_0} \times \binom{h_2}{h_2-h'_2}\alpha^{h_2-h'_2}(1-\alpha)^{h'_2}}{\sum_{l=0, l \leq k}^k \binom{h_0}{l}(1-\beta)^l\beta^{h_0-l} \times \binom{h_2}{k-l}\alpha^{k-l}(1-\alpha)^{h_2-(k-l)}} \quad \text{s.t.} \quad \|\mathbf{h}' - \mathbf{h}\|_1 = k \quad (3.9)$$

$$P(X_{n+1}^j = \mathbf{h}'' \mid \ddot{X}_{n+\epsilon}^j = \mathbf{h}', X_n^j = \mathbf{h}, o_n = O_k) = \begin{cases} \sum_{\mathbf{h}' \in \Omega^{\gamma_j}} \binom{h'_0}{h'_0-h''_0} \bar{p}^{h'_0-h''_0} (1-\bar{p})^{h''_0} \binom{h'_1}{h'_1-h''_1} q^{h'_1-h''_1} (1-q)^{2h'_1-h''_1} \\ 0, \quad \text{otherwise} \end{cases} \quad (3.10)$$

$$P(X_{n+1}^j = \mathbf{h}'' \mid X_n^j = \mathbf{h}, o_n) = \sum_{\mathbf{h}' \in \Omega^{\gamma_j}} P(X_{n+1}^j = \mathbf{h}'' \mid \ddot{X}_{n+\epsilon}^j = \mathbf{h}', X_n^j = \mathbf{h}, o_n = O_k) P(\ddot{X}_{n+\epsilon}^j = \mathbf{h}' \mid X_n^j = \mathbf{h}, o_n = O_k) \quad (3.11)$$

where $\|\cdot\|_1$ refers to the Manhattan norm. Using the forward algorithm, we can calculate the belief state at a certain time, $\mathbf{h}$, given the history of observations as the following:

$$P(X_1^j = \mathbf{h}'' \mid O = o_0) = \sum_{\mathbf{h} \in \Omega^{\gamma_j}} P(X_1^j = \mathbf{h}'' \mid X_0^j = \mathbf{h}, o_0) \quad (3.12)$$

$$\begin{aligned} P(X_{n+1}^j = \mathbf{h}'' \mid O = o_1, \dots, o_n) \\ = \sum_{\mathbf{h} \in \Omega^{\gamma_j}} P(X_{n+1}^j = \mathbf{h}'' \mid X_n^j = \mathbf{h}, o_n) P(X_n^j = \mathbf{h} \mid o_1, \dots, o_{n-1}) \quad \forall n \geq 1 \end{aligned} \quad (3.13)$$

3.3.3 MDP Model

We develop a discrete-time finite-horizon MDP model that captures MRSA transmission and progression in each isolated room using an HMM to determine the optimal testing decisions for these rooms. The transition probabilities and rewards are assumed to be

stationary. The time horizon is divided into days and testing decisions are made at the beginning of each day in the isolation. In our model, the current decision epoch is denoted by $t \in \mathbf{T} = \{0, 1, \dots, T\}$, where T represents the length of the decision horizon.

States: We denote the state of the MDP model at time t by $\mathbf{s}_t = (\mathbf{Q}_t^1, \mathbf{Q}_t^2, \dots, \mathbf{Q}_t^\omega, \lambda_t) \in \mathbf{S}$, where $\mathbf{S} = \{(\mathbf{Q}^1, \mathbf{Q}^2, \dots, \mathbf{Q}^\omega, \lambda) \mid \mathbf{Q}^j \in \mathbb{N}_0^{2 \times \delta} \text{ for } j = 1, 2, \dots, \omega; \lambda \in \mathbb{R}\}$. Here, each $\mathbf{Q}^j$ is a matrix of the form $\mathbf{Q}^j = \begin{bmatrix} \mathbf{q}_1^j & \mathbf{q}_2^j & \dots & \mathbf{q}_\delta^j \end{bmatrix}$, where $\mathbf{q}_i^j = \begin{bmatrix} n_i^j \\ t_i^j \end{bmatrix}$ is a column vector indicating that n_i^j exposed roommates in the j th isolated room spent t_i^j days together before the i th PCR test. Additionally, λ represents the rate of recognizing a new MRSA case in a room.

Based on the room composition $\mathbf{Q}^j$ for room j , which is part of the MDP state, the health statuses of the roommates are not directly observable, making the system partially observable. Therefore, to infer the hidden health states of the roommates after a certain number of tests, we can construct an HMM for room j that tracks the progression of these health states over time. The HMM captures the underlying dynamics of the unobserved health states, while the MDP governs the system's observable state transitions and actions. The steps to construct the HMM and calculate the probability of the roommates being in a particular health state after a series of tests for a particular room are as follows:

- *Step 1:* Identify the number of roommates in the room after the most recent test, denoted as n_σ , where $\sigma = \max_{i \in \mathbf{I}} \{i : n_i^j = \mathbf{q}_i^j(1) \neq 0, t_i^j = \mathbf{q}_i^j(2) \neq 0\}$.
- *Step 2:* Construct the HMM, X_n^j , for room j .

- *Step 3:* Calculate the initial probability distribution (Eq.(3.2)), transition and observation probabilities (Eq.(3.8), Eq.(3.10), Eq.(3.9)) .
- *Step 4:* Calculate the belief state at certain time in isolation, $n = \sum_{i=1}^{\sigma} t_i^j$ (Eq. (3.13)).

Actions: Given the state $\mathbf{s}_t$, an action $a_t^j \in \mathbf{A}^j(\mathbf{Q}_t^j) \subset \mathbf{A} = \{\text{no test (NT)}, \text{test and do not release the test negatives (TDR)}, \text{test and release the test negatives (TR)}\}$ needs to be taken for each isolated room j . If the current test is the last one allowed, or the roommates have reached the maximum number of days in isolation, the only possible action is to test and release the roommates (TR). Otherwise, there are three possible actions available for each room at time t . The action for state $\mathbf{s}_t \in \mathbf{S}$ is represented as $\mathbf{a}_t = (a_t^1, a_t^2, \dots, a_t^\omega) \in \mathbf{A}_t = \cup_{j \in \mathbf{J}} \mathbf{A}^j(\mathbf{Q}_t^j)$ which specifies the actions chosen for each isolated room in the hospital at time t . The action space for room $j \in \mathbf{J}$ is defined in Equation 3.14.

$$\mathbf{A}^j(\mathbf{Q}_t^j) = \begin{cases} TR, & \text{if } \sigma = \delta \text{ or } \sum_{i=1}^{\sigma} t_i^j = N \\ \mathbf{A}, & \text{otherwise} \end{cases} \quad (3.14)$$

where $\sigma = \max_{i \in \mathbf{I}} \{i : n_i^j = \mathbf{q}_i^j(1) \neq 0, t_i^j = \mathbf{q}_i^j(2) \neq 0\}$, δ is the upper limit on the number of tests allowed per room, and N is the maximum isolation duration.

Transition Probabilities: Transition probabilities depend on changes in the composition of each isolated room. The composition of room j in the next period is affected by whether the exposed roommates in that room are tested in the current period, as shown in Equation 3.15. If the roommates are not tested ($a_t^j = NT$), they will spend one more day together in isolation, increasing the duration count by one. If the roommates are tested but the test negatives are not released ($a_t^j = TDR$), the room composition changes based on

the test result. The test index is incremented, resulting in $\mathbf{q}_{i+1}^j = (n_{i+1}^j, 1)$ where n_{i+1}^j represents the test negatives. If the roommates are tested and the test negatives are released ($a_t^j = TR$), two scenarios can occur. For the first room to take this action, identified by $r = \arg \min_j \{j \mid a_t^j = TR\}$, the room composition will update based on whether a new index MRSA case is detected or will become empty. For all other rooms, $j \neq r$, where the action is test and release, the room will become empty, assuming at most one new index case is detected at any given period.

$$\mathbf{Q}_{t+1}^j = \begin{cases} \mathbf{Q}_t^j + \mathbf{E}_i \begin{bmatrix} 0 \\ 1 \end{bmatrix}, & \text{if } a_t^j = NT, \sigma = i \\ \mathbf{Q}_t^j + \mathbf{E}_{i+1} \begin{bmatrix} n_{\sigma+1}^j \\ 1 \end{bmatrix}, & \text{if } a_t^j = TDR, \sigma = i \\ \mathbf{E}_1 \begin{bmatrix} H^{\gamma_j} \\ 0 \end{bmatrix} \text{ or } \mathbf{0}_{2 \times \delta}, & \text{if } a_t^j = TR, \sigma = i, j = r \\ \mathbf{0}_{2 \times \delta}, & \text{if } a_t^j = TR, \sigma = i, j \neq r \end{cases} \quad (3.15)$$

where $\mathbf{E}_\sigma \begin{bmatrix} a \\ b \end{bmatrix}$ represents a $2 \times \delta$ matrix with the σ th column given by $\begin{bmatrix} a \\ b \end{bmatrix}$ and all other entries being zero.

Let $P(\mathbf{Q}_{t+1}^j \mid \mathbf{Q}_t^j, a_t^j)$ denote the probability that the room composition at time $t+1$ will be $\mathbf{Q}_{t+1}^j$ given the room condition and action at time t . The corresponding probabilities are given by:

$$P(\mathbf{Q}_{t+1}^j | \mathbf{Q}_t^j, a_t^j) = \begin{cases} 1, & \text{if } a_t^j = NT \\ P(o_n = O_k), & \text{if } a_t^j = TDR, \quad k = \mathbf{q}_{i+1}^j(1) - \mathbf{q}_i^j(1) = n_{i+1}^j - n_i^j \\ (1 - e^{-\lambda})p_{\gamma_j} & \text{if } a_t^j = TR, \sigma = i, j = r, \mathbf{Q}_{t+1}^j = \mathbf{E}_1 \begin{bmatrix} H^{\gamma_j} \\ 0 \end{bmatrix} \\ e^{-\lambda} & \text{if } a_t^j = TR, \sigma = i, j = r, \mathbf{Q}_{t+1}^j = \mathbf{0}_{2 \times \delta} \\ 1, & \text{if } a_t^j = TR, \sigma = i, j \neq r \\ 0, & \text{otherwise} \end{cases} \quad (3.16)$$

where $P(O_k)$ denotes the probability that k people are tested positive. Given the transition probabilities for each room, the transition probability from state $\mathbf{s}_t$ to $\mathbf{s}_{t+1}$, given action $\mathbf{a}_t$ will be the product of the individual room probabilities since the transitions between rooms are independent:

$$P(\mathbf{s}_{t+1} | \mathbf{s}_t, \mathbf{a}_t) = P((\mathbf{Q}_{t+1}^1, \dots, \mathbf{Q}_{t+1}^\omega, \lambda_{t+1}) | (\mathbf{Q}_t^1, \dots, \mathbf{Q}_t^\omega, \lambda_t), \mathbf{a}_t) = \prod_{j=1}^{\omega} P(\mathbf{Q}_{t+1}^j | \mathbf{Q}_t^j, a_t^j) \quad (3.17)$$

We assume that the recognition of a new index MRSA case follows a Poisson distribution with a particular rate λ per day as employed in several existing studies modeling MRSA spread and testing ([McBryde et al. 2007](#), [Barnes et al. 2010](#), [Shenoy et al. 2018](#)). When exposed roommates are released from isolation, missed cases (false-negative) can lead to future transmissions, increasing this rate. As a result, λ depends on the contribution of missed cases and is included as part of the state definition, i.e., $\mathbf{s}_t = (\mathbf{Q}_t^1, \mathbf{Q}_t^2, \dots, \mathbf{Q}_t^\omega, \lambda_t)$. To capture the varying effect of this rate, we introduce a set of different values into the

model $\lambda_t \in \mathbf{\Lambda} = (\lambda_r, \lambda_1, \dots, \lambda_\psi)$. We calculate the expected number of missed cases for each isolated room when the action is to test and release the patients with negative test results (TR) to determine the values of these different rates.

$$E[\mathbf{Q}^j, a^j] = \begin{cases} \sum_{k=1}^{n_\sigma^j} P(o_n = O_k) \sum_{m=1}^{n_\sigma^j - k} m P(F^- = m | o_n = O_k), & \text{if } a_t^j = TR \\ 0, & \text{otherwise} \end{cases}$$

The total expected number of missed cases for a state given the action is then:

$$E[\mathbf{s}, \mathbf{a} = (a_t^j)_{j=1}^\omega] = \sum_{j=1}^\omega E[\mathbf{Q}^j, a^j] \quad \forall \mathbf{s} \in \mathbf{S}, \mathbf{a} \in \mathbf{A} \quad (3.18)$$

We calculate the expected number of missed cases for all possible state and action combinations, set $\Psi = \{E[\mathbf{s}, \mathbf{a}] \mid \mathbf{s} \in \mathbf{S}, \mathbf{a} \in \mathbf{A}, j = 1, 2, \dots, \omega\}$. Using the Jenks natural breaks classification method, we classify them into ψ groups, $\Phi_1, \dots, \Phi_\psi$. This method aims to minimize the variance within each group by clustering the points with similar expected numbers of missed cases while maximizing the variance between different groups. Finally, we compute the contribution of missed cases to the rate for each set $\Phi_1, \dots, \Phi_\psi$ using the mean of the group as follows:

$$\lambda_\kappa = \lambda_r + \mu \frac{1}{|\Phi_\kappa|} \sum_{e \in \Phi_\kappa} e \quad \forall \kappa = 1, \dots, \psi \quad (3.19)$$

where λ_r is the regular rate and $1/\mu$ refers to the mean number of days until a missed case is recognized.

Reward Functions: We consider two objective functions: minimizing the expected loss

of QALYs and the expected number of MRSA colonizations. For the first objective function, we consider the disutility values associated with adverse health states or interventions including infection, isolation, testing and decolonization to balance competing interests. We assume half the decision interval length will be spent in isolation until test results become available. Let $d^j(\mathbf{Q}_t^j, a_t^j)$ represent the disutility for room j based on its condition and chosen action. If the action is no testing, the expected loss of QALYs for room j will be the sum of the disutility of staying in isolation for all exposed roommates. If the action is TDR, the expected loss of QALYs for room j will be the sum of the disutility of MRSA decolonization for true positive cases, the disutility of isolation for those who are tested negative, disutility of staying in isolation until the maximum isolation duration for false-positive cases, and the disutility of staying in isolation for all roommates until the test results are released. Finally, if the action is to TR for room j , the total expected loss of QALYs will be the sum of the disutility of MRSA decolonization for true positive cases, the disutility of staying in isolation until the maximum isolation duration for false-positive cases, the disutility of infection for false-negative cases (i.e., missed cases), and the disutility of staying in the isolation for all roommates until the test results are released.

$$d^j(\mathbf{Q}_t^j, a_t^j) =$$

$$\left\{ \begin{array}{ll}
d_{iso} n_{\sigma}^j, & \text{if } a_t^j = NT, \\
\sum_{k=0}^{n_{\sigma}^j} P(O_k) \left(d_{test}(n_{\sigma}^j + k) + d_{iso} n_{\sigma}^j - 0.5 d_{iso} k + d_{col} \sum_{\ell=0}^k \ell P(T^+ = \ell | O_k) \right. \\
\quad \left. + \left(N - \sum_{i=1}^{\sigma} t_i^j - 0.5 \right) d_{iso} \sum_{\ell=0}^k (k - \ell) P(T^+ = \ell | O_k) \right), & \text{if } a_t^j = TDR, \\
\sum_{k=0}^{n_{\sigma}^j} P(O_k) \left(d_{test}(n_{\sigma}^j + k) + 0.5 d_{iso} n_{\sigma}^j + d_{col} \sum_{\ell=0}^k \ell P(T^+ = \ell | O_k) \right. \\
\quad \left. + \left(N - \sum_{i=1}^{\sigma} t_i^j - 0.5 \right) d_{iso} \sum_{\ell=0}^k (k - \ell) P(T^+ = \ell | O_k) \right. \\
\quad \left. + d_{inf} \sum_{m=0}^{n_{\sigma}^j - k} m P(F^- = m | O_k) \right), & \text{if } a_t^j = TR.
\end{array} \right. \quad (3.20)$$

The second objective is to minimize the number of MRSA colonizations which is more important from the clinical perspective. Let $r^j(\mathbf{Q}_t^j, a_t^j)$ denote the MRSA colonizations for room j . On day 0, MRSA colonizations are defined by the number of undetectable and detectable colonized roommates (primary transmissions) in room j . For subsequent periods, where $n = \sum_{i=1}^{\sigma} t_i^j \neq 0$, MRSA colonizations are calculated as the difference in the number of non-colonized roommates between consecutive periods to identify newly transmitted cases (secondary transmissions).

$$r^j(\mathbf{Q}_t^j, a_t^j) = \begin{cases} \sum_{\mathbf{h} \in \Omega^{\gamma_j}} P(X_{n-1}^j = \mathbf{h}) (h_1 + h_2), & \text{if } n = 0 \\ \sum_{\mathbf{h} \in \Omega^{\gamma_j}} P(X_{n-1}^j = \mathbf{h}) h_0 - \sum_{\mathbf{h} \in \Omega^{\gamma_j}} P(X_n^j = \mathbf{h}) h_0, & \text{if } n \neq 0 \end{cases} \quad (3.21)$$

The optimal solution for the MDP model can be obtained by solving the following set

of Bellman equations ([Puterman 2014](#)):

$$V_t^*(\mathbf{s}) = \min_{\mathbf{a}_t \in \mathbf{A}_t} \left\{ \sum_{j \in \mathbf{J}} d^j(\mathbf{Q}_t^j, a_t^j) + \nu \sum_{\mathbf{s}' \in \mathbf{S}} P(\mathbf{s}' | \mathbf{s}_t, \mathbf{a}_t) V_{t+1}^*(\mathbf{s}') \right\} \quad (3.22)$$

$$Y_t^*(\mathbf{s}) = \min_{\mathbf{a}_t \in \mathbf{A}_t} \left\{ \sum_{j \in \mathbf{J}} r^j(\mathbf{Q}_t^j, a_t^j) + \nu \sum_{\mathbf{s}' \in \mathbf{S}} P(\mathbf{s}' | \mathbf{s}_t, \mathbf{a}_t) Y_{t+1}^*(\mathbf{s}') \right\}, \quad (3.23)$$

where $\nu \in [0, 1]$ is the discount factor introduced to consider the time value of the future rewards.

3.3.4 Secondary Performance Metrics

Although the primary objectives are to minimize the loss of QALYs and the number of colonizations, we also assess secondary performance metrics, such as the expected total MRSA management cost, the expected number of missed cases, and the number of false positive cases. Evaluating these metrics is crucial for identifying testing protocols that are both cost-efficient and effective in improving health outcomes.

We define the total cost incurred for room j given its condition and chosen action as $c^j(\mathbf{Q}_t^j, a_t^j)$. If the action is *NT*, the expected total cost will be the cost of isolating all exposed roommates. If the action is *TDR*, the expected total cost includes the treatment cost for true positive cases, isolation cost for patients who test negative, cost of remaining in isolation until the maximum isolation duration and cost of confirmatory culture for false-positive cases, and the cost of isolation and PCR tests for all roommates until test results are available until the test results are released. Finally, if the action is to *TR*, the total cost includes the treatment cost for true positive cases, cost of remaining in isolation until

the maximum isolation duration and cost of confirmatory culture for false-positive cases, cost of treatment for false-negative cases (i.e., missed cases), and the cost of isolation and PCR test for all roommates until test results are available. We derive $c^j(\mathbf{Q}_t^j, a_t^j)$ as follows:

$$c^j(\mathbf{Q}_t^j, a_t^j) = \begin{cases} c_{iso}n_\sigma^j, & \text{if } a_t^j = NT, \\ \sum_{k=0}^{n_\sigma^j} P(O_k) \left(c_{iso}n_\sigma^j - 0.5c_{iso}k + c_{PCR}n_\sigma^j + c_{col} \sum_{\ell=0}^k \ell P(T^+ = \ell | O_k) \right. \\ \quad \left. + ((N - \sum_{i=1}^\sigma t_i^j - 0.5)c_{iso} + c_{cul}) \sum_{\ell=0}^k (k - \ell) P(T^+ = \ell | O_k) \right), & \text{if } a_t^j = TDR, \\ \sum_{k=0}^{n_\sigma^j} P(O_k) \left(0.5c_{iso}n_\sigma^j + c_{col} \left(\sum_{\ell=0}^k \ell P(T^+ = \ell | O_k) + \sum_{m=0}^{n_\sigma^j-k} m P(F^- = m | O_k) \right) \right. \\ \quad \left. + ((N - \sum_{i=1}^\sigma t_i^j - 0.5)c_{iso} + c_{cul}) \sum_{\ell=0}^k (k - \ell) P(T^+ = \ell | O_k) + c_{PCR}n_\sigma^j \right), & \text{if } a_t^j = TR. \end{cases} \quad (3.24)$$

We define $z^j(\mathbf{Q}_t^j, a_t^j)$ and $f^j(\mathbf{Q}_t^j, a_t^j)$ to represent the expected number of missed cases and false-positive cases, respectively, for room j . These metrics are calculated as follows:

$$z^j(\mathbf{Q}_t^j, a_t^j) = \begin{cases} \sum_{m=0}^{n_\sigma^j-k} m P(F^- = m | o_n = O_k), & \text{if } a_t^j = TR \\ 0, & \text{otherwise} \end{cases} \quad (3.25)$$

$$f^j(\mathbf{Q}_t^j, a_t^j) = \begin{cases} \sum_{\ell=0}^k (k - \ell) P(T^+ = \ell | o_n = O_k), & \text{if } a_t^j = TR \text{ or } TDR \\ 0, & \text{otherwise} \end{cases} \quad (3.26)$$

To calculate the performance metrics under a given testing protocol $\mathbf{a}_t$, we assume the

system is initially empty at the beginning of the time horizon. For example, the total MRSA management cost under this protocol is calculated as follows:

$$C_t(\mathbf{s} = (\mathbf{0}, \dots, \mathbf{0}, \lambda_0), \mathbf{a}_t) = \sum_{j \in \mathbf{J}} c^j(\mathbf{Q}_t^j, a_t^j) + \sum_{\mathbf{s}' \in \mathbf{S}} P(\mathbf{s}' | \mathbf{s}_t, \mathbf{a}_t) C_{t+1}(\mathbf{s}', \mathbf{a}_t) \quad (3.27)$$

This formulation incorporates both immediate and future costs under the specified protocol, starting from an initially empty system state. The expected numbers of missed cases and false positives can be calculated similarly.

3.4 Numerical Results

In this section, we first present the optimal testing decisions using the base case parameters provided in Table 3.2. Then, we compare the performance of the optimal testing strategies with those of the current guidelines and some practical testing protocols. The current MRSA surveillance guideline among the exposed roommates is 7-day isolation with day 0 and day 6 culture tests (Cult0+Cult6). In 2015, the practice at the Grand River Hospital in Ontario, from which we derived some of our data, changed from guideline to 3-day isolation with day 0 culture and day 3 PCR test to reduce the isolation period. Finally, we perform sensitivity analyses on the various model parameters. In our numerical experiments, we limit the number of rooms where isolation can happen to a maximum of two and set the rate of recognizing a new index case in a room to 0.05 per day, ensuring that the probability of having more than two rooms in isolation is negligible. In addition to that, we consider two

different rates corresponding to low and high-risk groups, with the detection rate of a new index case varying based on the risk level of missed cases. Also, the exposed roommates undergo a maximum of two PCR tests during isolation, with a maximum isolation period of seven days, aligning with the existing guidelines recommending two follow-up tests (PIDAC 2013).

Table 3.2: Input data.

Description	Base-case value	Estimation method and data source
Room setting		
Percentage of cohort rooms (4 people)	80%	Lin et al. (2023)
Percentage of semi-private rooms (2 people)	20%	Lin et al. (2023)
MRSA progression and transmission parameters		
Prevalence at the beginning of isolation	7.48%	Lin et al. (2023)
Transmission probability during the isolation (per patient per day)	0.84%	Lin et al. (2023)
Probability of being colonized detectable at the beginning of isolation	43.22%	Derived based on data from IPAC of the acute care site and Ng et al. (2012)
Probability of transition from colonized undetectable to detectable stage	25.3%	Calibration based on data from IPAC of the acute care site and Ng et al. (2012)
Test characteristics		
Sensitivity of culture test	69.4%	IPAC of the acute care site
Specificity of culture test	100%	Tübbicke et al. (2012b,a)
Sensitivity of PCR test	80.6%	IPAC of the acute care site
Specificity of PCR test	97.5%	Tübbicke et al. (2012b,a)
Turnaround time of culture test	24h	Tübbicke et al. (2012a), Nyman et al. (2011), Lee et al. (2011)
Turnaround time of PCR test	1-2 h	Tübbicke et al. (2012a), Nyman et al. (2011), Lee et al. (2011)
Costs		
Cost of a culture test	\$13.85	Roth et al. (2016a), Tübbicke et al. (2012a), Nyman et al. (2011), Lee et al. (2011)
Cost of a PCR test	\$41.11	Roth et al. (2016a), Tübbicke et al. (2012a), Nyman et al. (2011), Lee et al. (2011)
Cost of isolation (per patient per day)	\$73.31	Roth et al. (2016a), Tübbicke et al. (2012a), Kim et al. (2001)
Cost of MRSA colonization (per patient)	\$1,316.41	Roth et al. (2016a), Kim et al. (2001)
Disutility values		
Disutility of isolation (per patient per day)	0.0039	Codella (2014)
Disutility of testing (per patient per test)	0.01	Singer and Younossi (2001)
Disutility of decolonization (per patient)	0.253	Whittington et al. (2017), Hong et al. (2018)
Disutility of missed cases (per patient)	0.386	Lee et al. (2010), Dymond et al. (2020)

Table 3.2 presents the input parameters, their corresponding values, and the sources utilized in the numerical analyses. We obtain the room settings, room-type distributions, prevalence and disease transmission probability from a previous simulation study (Lin et al. 2023), which utilizes both clinical data and information from the literature. Constant test sensitivities are estimated using the confirmation test results of cases with known MRSA colonization from the IPAC department of the acute care site. Test specificities, turnaround times, and some cost parameters are obtained from the existing clinical studies and cost-effectiveness analyses (Tübbicke et al. 2012a,b). Additional cost parameters are synthesized from multiple sources on MRSA management, as detailed in Lin et al. (2023). We derived the probability of being colonized detectable at the beginning of isolation using a constant culture test sensitivity and benchmark statistic from a retrospective study conducted at North York General Hospital (NYGH), ON-Canada; a similar-sized Ontario community teaching hospital to our acute care site (Ng et al. 2012). The study (Ng et al. 2012) reported an 8% cumulative rate of MRSA colonization as well as 30%, 56%, and 55% MRSA detection rates in NYGH for culture tests at the beginning and end of the isolation period, and a PCR test in the middle of the isolation, respectively. Given the constant culture sensitivity of 69.4% and the reported detection rate of 30% at the beginning of the isolation period (0-1 day post exposure), the probability of being colonized at the beginning of isolation is calculated as 43.22% ($30/69.4$). Additionally, the transition probability from undetectable to detectable colonized state is estimated through model calibration using benchmark statistics from Ng et al. (2012) and data from the IPAC of the acute care site. The calibration process includes specifying a plausible search interval for the parameter, discretizing the interval into candidate values, and systematically evaluating these values

to identify the one that produces model outputs matching the selected benchmark statistics with the minimum mean squared error. We consider the rates in [Ng et al. \(2012\)](#) as benchmark statistics and determine the calibrated model parameter estimating these benchmark statistics with minimum mean squared error as 25.3%.

Disutility parameters quantify the negative impact on patients' quality of life due to various interventions and complications related to MRSA management. Disutility values are derived by synthesizing data from the literature. [Codella \(2014\)](#) investigated optimal control strategies for *C. difficile* infections, including the disutility associated with patient isolation. While centered on *C. difficile*, the disutility due to the psychological impact of isolation applies to MRSA. [Singer and Younossi \(2001\)](#) analyzed the cost-effectiveness of screening for hepatitis C virus (HCV) in asymptomatic, average-risk adults, primarily using the ELISA test for initial screening and confirmatory PCR testing to verify positive results. Their assessment of the disutility associated with testing, which includes the physical discomfort of the test and the anxiety related to awaiting results, is adapted to MRSA testing for PCR. The disutility of MRSA decolonization is derived from [Whittington et al. \(2017\)](#) and [Hong et al. \(2018\)](#), who assessed the negative impact on patient quality of life due to the inconvenience, side effects, and adherence challenges associated with MRSA decolonization procedures. The disutility of missed MRSA cases is derived from studies by [Lee et al. \(2010\)](#) and [Dymond et al. \(2020\)](#), which evaluated the significant negative impact on patient quality of life, including the risk of developing more serious health complications, treatment and the associated psychological distress due to MRSA infections. Given that missed MRSA colonization can progress to infections, the disutility value for infection is used in this analysis.

We validate our model through a comparative analysis with an established, clinically validated simulation model (Lin et al. 2023). Lin et al. (2023) evaluated the performance of a few surveillance testing and isolation strategies that are in practice for the exposed roommates of an index MRSA case in a medium-sized Canadian hospital using a simulation model. Employing the same parameter settings designed for the small hospital considered in this study, we calculate several performance metrics such as the number of MRSA colonizations, transmissions during the isolation and missed cases. We observe that the outcomes of our model under the current protocol (Cult0+Cult6) and the findings reported by Lin et al. (2023) are very close, as presented in Table 3.3.

Table 3.3: Comparison of the proposed MDP model and simulation model from Lin et al. (2023).

Performance measures	Simulation model (Cult0+Cult6)	MDP model (Cult0+Cult6)
Number of MRSA colonizations	8%	8%
MRSA transmissions before isolation	94%	94%
MRSA transmissions during isolation	6%	6%
True positives at the first testing	30%	28%
True positives at the second testing	38%	41%
Number of missed MRSA cases	31%	31%

3.4.1 Optimal MRSA Testing Decisions

We first illustrate the optimal testing and isolation decisions derived from our model to provide insights into their structures and dynamic and complex nature. Figure 3.2 shows the optimal testing decisions to minimize the number of MRSA colonizations. For situations involving a single cohort room (first branch of Figure 3.2), the optimal testing

strategy includes conducting an initial testing of roommates on day one, followed by a second testing for those who test negative initially, on day two. Given the potential for disease transmission in the cohort room, the first testing is performed earlier to detect and remove the colonized cases promptly to prevent secondary transmissions. To ensure the accurate detection of any positive cases and mitigate the risk of missed cases, roommates are kept in isolation for an additional day before the second test. Note that new index cases can be recognized in cohort or semi-private rooms on day 1. In these cases, the optimal actions may differ. These events are omitted from the figure for ease of representation.

If a new index case is recognized in a semi-private room on day 1 after detecting an index case in a cohort room on day 0 (i.e., the second branch of Figure 3.2), the initial testing of roommates in the cohort room is scheduled for day 5. Those testing negative initially required to remain in isolation for an extra day and take the second test to further reduce the risk of missing MRSA cases leading to more primary transmissions later on. Given the risk of secondary transmissions from undetected MRSA carriers, an extra day of isolation is deemed sufficient before the second test. In the semi-private room, the initial testing occurs on day 5 (i.e., 4 days after isolation starts in the semi-private room), followed by a second test one day later if the first test yields a negative result. Note that the optimal solution in the third branch (e.g., having a new index case in a cohort room on day 1) is almost identical to the one in the second branch, except both rooms receive the initial and secondary testing on the same days.

When the objective is to minimize the expected loss of QALYs, the optimal testing strategies differ from those minimizing the expected MRSA colonization. When an index case is recognized in a cohort room on day 0 (the first branch of Figure 3.3), the optimal

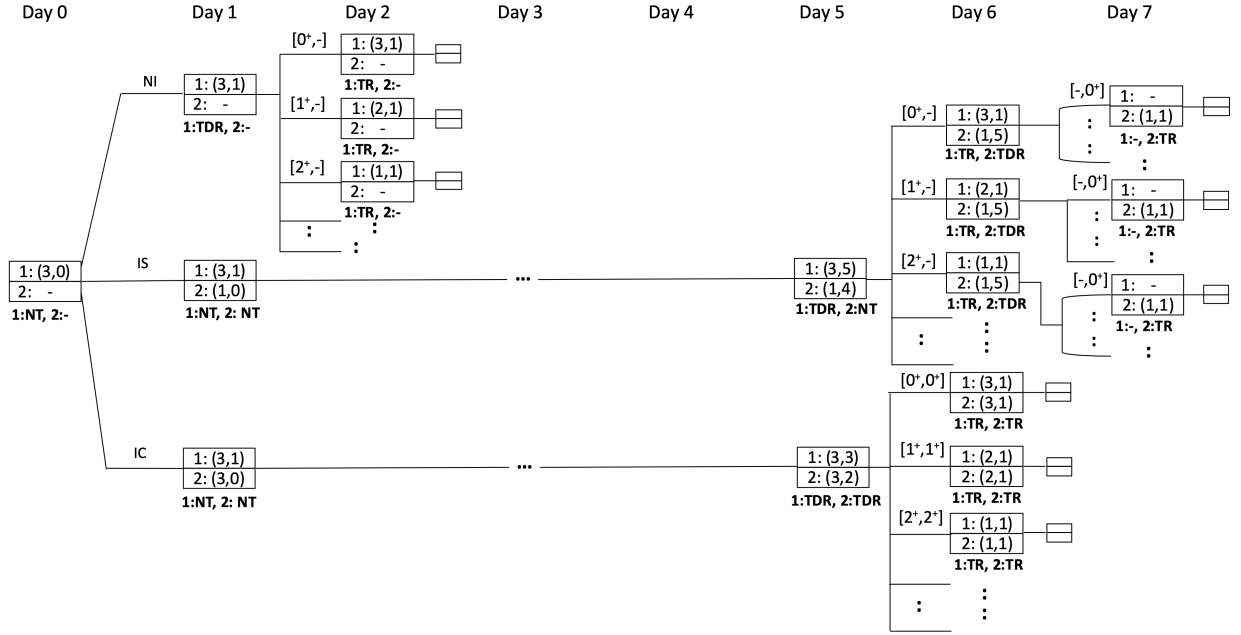


Figure 3.2: Optimal testing decisions to minimize MRSA colonizations with the regular new index case detection rate in the base case scenario. NI: No new index case recognition, IS: New index case recognition in a semi-private room, IC: New index case recognition in a cohort room, NT: No test, TDR: Test and do not release test negatives, TR: Test and release test negatives

action is delaying the testing of exposed roommates to day 3. If no new index case is recognized, the optimal solution is to test the exposed roommates on day 3 and release the roommates with negative test results. Note that the optimal strategy applies only one test in this case to reduce the disutility of testing and delays the testing time to day 3 to increase its accuracy.

If a new index case is detected in a semi-private room on day 1 (see the second branch of Figure 3.3), the initial testing for the exposed roommates in the cohort room is delayed to day 4. However, unlike in the first branch of the figure, the optimal protocol requires

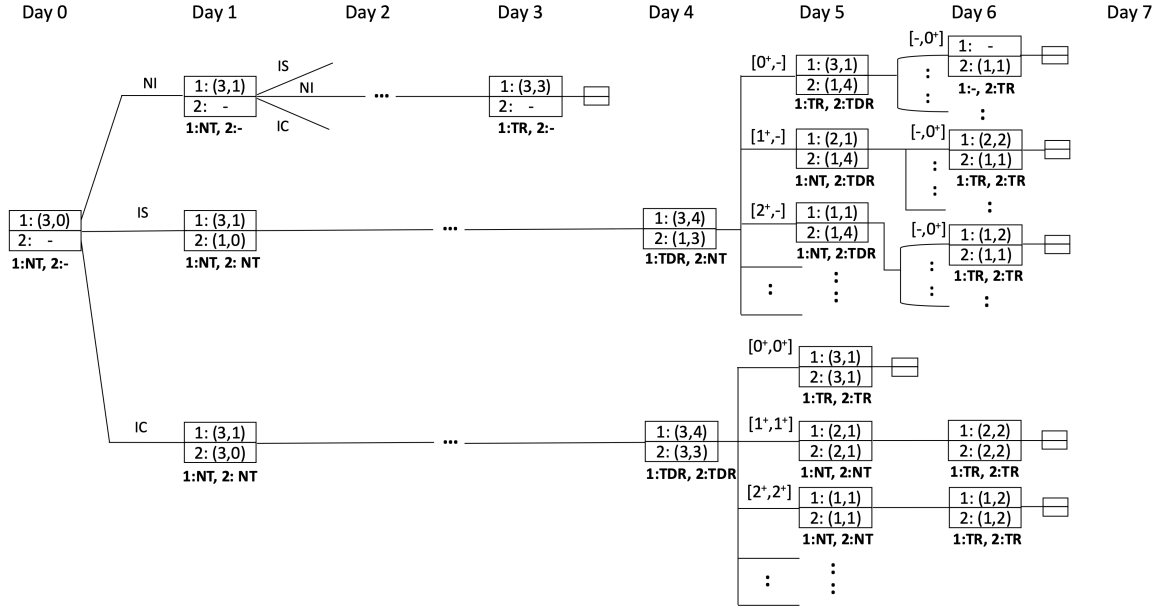


Figure 3.3: Optimal testing decisions to minimize loss of QALYs with the regular new index case detection rate in the base case scenario.

keeping the test negatives in isolation so that a second test could improve the overall detection rate and prevent further transmissions due to missed cases. The testing strategy in branch 2 is more aggressive than in branch 1 because there are more patients at risk in the prior case. If the first test detects no positive cases, the roommates are kept in isolation for an additional day before being released following a second test. However, if one or two exposed roommates test positive, the remaining roommates, who tested negative, stay in isolation for an extra two days before undergoing the second test. This is done again to improve the overall detection rate given the higher risk of exposure to undetected colonization cases in the first four days. Normally extending the isolation period also increases the risk of secondary transmissions; however, this risk is relatively

lower in the above cases as some or most of the positive individuals would be removed by the first test. For the second room (i.e., semi-private), the first test occurs on day 4. If the result is negative, the patient stays in isolation for one more day before undergoing the second test. Note that the optimal solution in the third branch (e.g., having a new index case in a cohort room) is almost identical to the one in the second branch.

Figures 3.2 and 3.3 show that the optimal testing decisions depend on the composition (i.e., number and types) of the isolated rooms and test results observed so far leading to a highly dynamic surveillance protocol. While the optimal strategy reduces the surveillance duration when fewer roommates are isolated in a fewer number of rooms, the exposure of a higher number of rooms or a higher number of roommates to index MRSA cases results in a prolonged isolation duration and a higher number of tests. Although achieving the best surveillance performance, implementing such a highly dynamic testing protocol may not be practical. However, identifying the optimal testing strategy and evaluating its performance is crucial for *i)* identifying to what extent the current practices can be improved, *ii)* specifying how existing practices can be adjusted to improve them based on the structure of the optimal strategies. For example, because having single cohort rooms would be the most likely scenario, applying the secondary/follow-up test earlier may help reduce the number of MRSA colonizations, while removing the initial PCR test may help decrease the QALY losses.

3.4.2 The Performance of the Optimal Testing Protocol Compared to the Current Practice

Table 3.4 shows the base-case performance of the MRSA surveillance with the existing guideline (Cult0+Cult6), current practice (i.e., Cult0+PCR3), and optimal testing decisions for both objective functions. Effectiveness of Cult0+PCR3, i.e., the current practice in our acute care hospital, has been reported in previous studies (Ng et al. 2012, Lin et al. 2023). Our results are in line with these previous findings. Cult0+PCR3 improves almost all health outcomes and reduces the costs at the expense of a slight increase in false positives, i.e., an average of 1.22 roommates being falsely identified with positive PCR results. Replacing Cult0+Cult6 with Cult0+PCR3 reduces the MRSA colonization due to secondary transmissions during isolation by 47.8%, which led to 1.9% fewer MRSA cases overall. While this replacement increases the testing cost as PCR is more expensive than culture tests, reducing the isolation costs by half compensates for the increased testing expenses. As a result, replacing Cult6 with PCR3 leads to a 34% reduction in total costs. These results support the acute care site’s decision to transition from a culture-based testing program to a culture plus PCR-based one. However, our results indicate that there is still potential for further improvement.

Compared to the current practice, the optimal testing protocols under both objective functions improve most health outcomes by either reducing or slightly increasing total cost. That is the number of colonizations and QALY losses associated with Cult0+PCR3 can be further reduced from 4.08 and 3.96 to 4.02 and 3.88, respectively, by the optimal surveillance strategies. Both optimal surveillance strategies achieve improvements to varying

Table 3.4: Comparison of the guideline, current practice, and the optimal MRSA testing protocols under the base-case scenario.

Performance measures	Guideline	Current Practice	Optimal Solution	
	Cult0+Cult6	Cult0+PCR3	Loss of QALYs	MRSA colonizations
Number of exposed roommates	52.54	52.91	51.83	52.54
Number of MRSA colonizations	4.16	4.08	4.05	4.02
Transmissions before isolation	3.93	3.96	3.88	3.93
Transmissions during isolation	0.23	0.12	0.18	0.09
True positives at the first testing	1.18	1.19	2.45	1.93
True positives at the second testing	1.70	1.48	0.16	0.67
Number of missed cases	1.28	1.40	1.44	1.43
Number of false positives	0	1.22	1.46	2.34
Testing cost	\$1,437	\$2,870	\$2,594	\$4,129
Isolation cost	\$26,225	\$13,614	\$15,383	\$11,691
MRSA colonization cost	\$5,481	\$5,366	\$5,337	\$5,294
Total cost	\$33,144	\$21,850	\$23,314	\$21,115
Total loss of QALYs	4.65	4.06	3.77	3.93

degrees across different performance measures. Specifically, the optimal testing protocol for minimizing the number of colonizations reduces the transmissions during isolation by 25% and isolation cost by 14.1% by shortening the isolation duration. Although incurring higher testing costs, the optimal protocol reduces the total cost by 3.4%. Compared to the current practice in the acute care site, the optimal testing protocols for minimizing the loss of QALYs and the number of colonizations reduce the loss of QALYs by 7.1% and 3.2%, respectively. However, these optimal protocols resulted in a higher number of false positives due to the imperfect specificity of the PCR test.

The performances of the optimal strategies show some similar patterns. Both strategies shorten the isolation duration, which is the main contributor to the reduced total cost. In addition, both optimal strategies reduce the total number of colonizations by limiting the exposure of roommates to unrecognized colonized patients, thereby reducing MRSA trans-

missions during isolation. However, the optimal protocols for different objective functions also follow different mechanisms to further improve the performance measures they focus on. For example, the optimal strategy for minimizing QALY losses delays the first testing to day 3 when only one cohort room is under isolation (a very likely scenario) and terminates the isolation. This increases the sensitivity of initial testing so that one test would be sufficient and QALY loss due to test disutility is prevented. On the other hand, for the same scenario, the optimal solution for minimizing the number of colonizations perform two tests in earlier days to separate potential MRSA cases from the other roommates. This ends up with fewer colonizations during isolation, thus limiting the overall transmissions and associated costs. By synthesizing the information from these patterns and mechanisms and those from the insights mentioned at the end of Section 4.1, we may be able to identify alternative practical strategies that can cover a portion (or most) of the performance gap between the guideline (or current practice) and the optimal strategies.

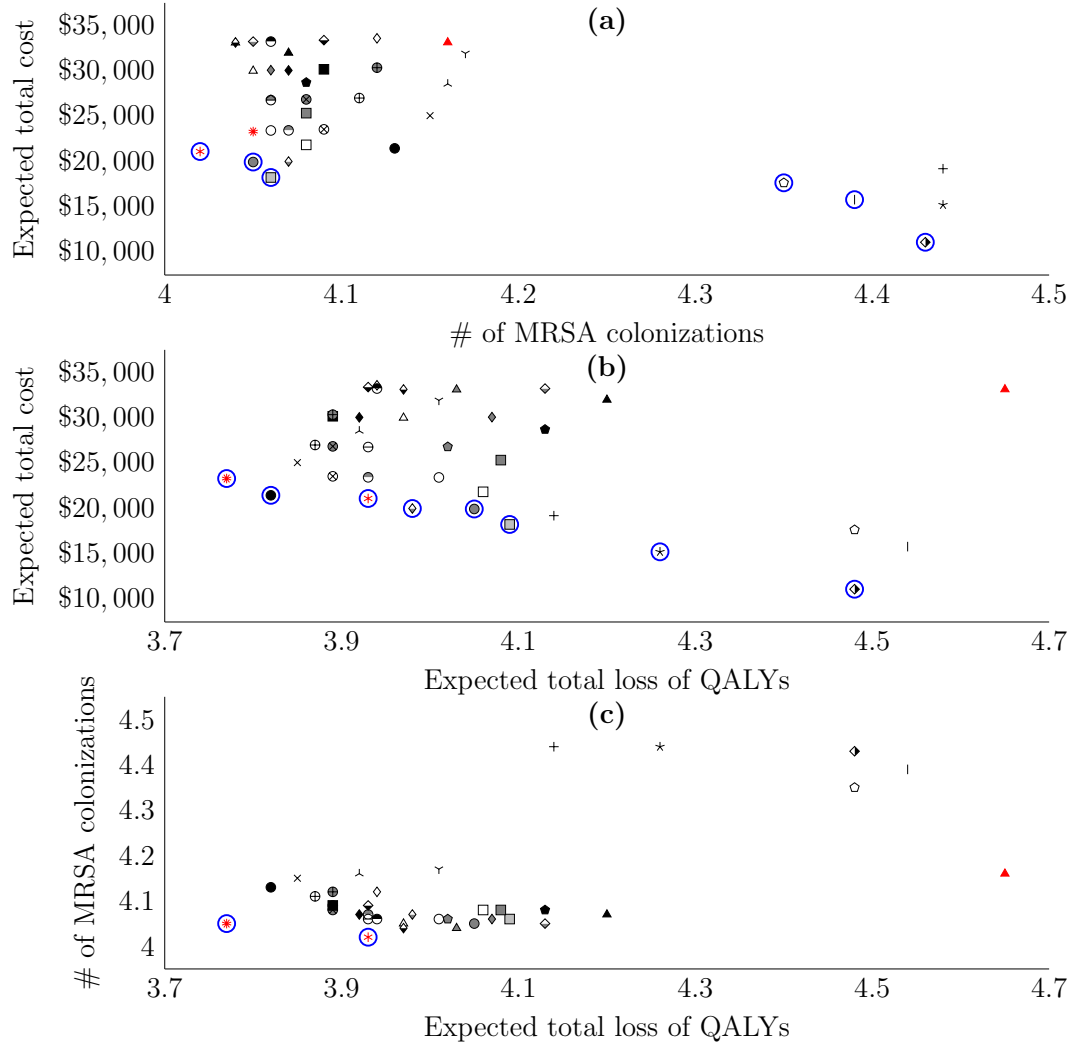
3.4.3 Comparison of the Optimal Testing Decisions with the Practical Surveillance Strategies

The controversy around best surveillance practices and the performance gap between the optimal protocols and guidelines can be addressed by focusing on practical surveillance strategies given that the optimal MRSA testing protocols from the MDP are highly dynamic and may be hard to implement in clinical settings. Thus, we evaluate various *practical MRSA testing protocols* deviating from the guidelines by adjusting the timing of initial and secondary PCR tests and highlight those with close-to-optimal performance.

While doing so, we explore some additional policy questions: *i*) what are the best/ideal days for conducting two PCR tests, *ii*) when and for which objective function applying a single test could be effective, and *iii*) is using culture (at day 0) and PCR test together effective? Reflecting the perspective of policymakers for infection control, we analyzed the performances of the considered practical testing protocols in the spectrum of the expected number of MRSA colonizations, total loss of QALYs, and total cost.

Figure 3.4 compares the performance of all possible practical testing protocols compared to the optimal and guideline protocols in the considered spectrums. Figure 3.4 shows that the current guidelines and practices can be improved in all spectrums. PCR0 can achieve the most cost savings with a slight improvement in QALY loss by eliminating the isolation process. However, this increases the number of colonizations significantly (Figure 3.4a), thus, not useful in improving health outcomes. On the other hand, the strategies closest to the bottom left corner of the frontier in Figure 3.4a (Cult0+PCR2 and PCR0+PCR2) provide a better balance of the considered metrics. Cult0+PCR2 and PCR0+PCR2 offer a close-to-optimal reduction in MRSA colonization while incurring 5.5% less cost than the optimal solution. Other two-test strategies such as PCR0+PCR6, PCR1+PCR6, PCR2+PCR6, and PCR1+PCR5 also achieve colonization reductions close to the optimal level by extending the isolation durations and increasing test accuracies. However, these strategies incur significantly higher isolation costs rendering them not cost-effective. Among the strategies involving only the day 0 culture test, Cult0+PCR2 performs relatively well in reducing colonization. Single-test strategies do not perform well in this spectrum.

In the loss of QALYs vs total cost spectrum (Figure 3.4b), the best practical strategy



* Optimal Protocol (QALY)	* Optimal Protocol (Col)	▲ Current Protocol	○ PCR0+PCR1	● PCR0+PCR2
○ PCR0+PCR3	● PCR0+PCR4	◆ PCR0+PCR5	◇ PCR0+PCR6	◇ PCR1+PCR2
○ PCR1+PCR3	⊖ PCR1+PCR4	△ PCR1+PCR5	▲ PCR1+PCR6	⊗ PCR2+PCR3
● PCR2+PCR4	◆ PCR2+PCR5	◇ PCR2+PCR6	⊕ PCR3+PCR4	■ PCR3+PCR5
● PCR3+PCR6	⊕ PCR4+PCR5	◇ PCR4+PCR6	◇ PCR5+PCR6	┆ Cult0+PCR1
□ Cult0+PCR2	□ Cult0+PCR3	■ Cult0+PCR4	● Cult0+PCR5	▲ Cult0+PCR6
◆ PCR0	* PCR1	+ PCR2	● PCR3	× PCR4
┆ PCR5	┆ PCR6			

Figure 3.4: Performance comparison of the optimal and practical testing protocols in terms of total loss of QALYs, total cost, and number of MRSA colonizations.

for minimizing the loss of QALYs is PCR3, which achieves a 7.9% reduction in total cost compared to the optimal solution. PCR4, another single-test strategy, also performs well in reducing QALY losses. PCR3+PCR4 is the two-test strategy with the lowest QALY losses; however, it does not perform as well as PCR3 and PCR4. Unfortunately, none of the practical strategies lies on the Pareto-efficient frontier of the QALY loss vs the number of colonizations spectrum (Figure 3.4c). Therefore, it is hard to achieve a middle ground between the performances of the optimal strategies by only using testing protocols with similar structures to the current guidelines and practices.

Table 3.5: Comparison of the current practice, optimal, and best practical testing protocols for the base-case scenario.

Performance measures	Current Practice	Loss of QALYs		MRSA Colonizations	
	Cult0+PCR3	Optimal Solution	PCR3	Optimal Solution	PCR0+PCR2
Number of exposed roommates	52.91	51.83	52.94	52.54	53.23
Number of MRSA colonizations	4.08	4.05	4.13	4.02	4.05
Transmissions before isolation	3.96	3.88	3.96	3.93	3.98
Transmissions during isolation	0.12	0.18	0.17	0.09	0.07
True positives at the first testing	1.19	2.45	2.46	1.93	1.39
True positives at the second testing	1.48	0.16	0	0.67	1.08
Number of missed cases	1.40	1.44	1.67	1.43	1.59
Number of false positives	1.22	1.46	1.22	2.34	2.43
Testing cost	\$2,870	\$2,594	\$2,193	\$4,129	\$4,297
Isolation cost	\$13,614	\$15,383	\$13,835	\$11,691	\$10,323
MRSA colonization cost	\$5,366	\$5,337	\$5,436	\$5,294	\$5,337
Total cost	\$21,850	\$23,314	\$21,464	\$21,115	\$19,957
Total loss of QALYs	4.06	3.77	3.82	3.93	4.05

We further evaluated the best-performing practical protocols, i.e. PCR0+PCR2 for the number of colonizations and PCR3 for the loss of QALYs, in terms of other performance metrics and presented the results in Table 3.5. PCR0+PCR2 is particularly effective in reducing MRSA colonizations by identifying and isolating primary transmissions as early as

possible, thereby minimizing further transmissions during isolation. Although this strategy leads to a slight increase in testing costs compared to the optimal solution, it ultimately reduces total isolation expenses by shortening the isolation duration. PCR3 resulted in a lower QALY loss compared to the other practical protocols because of applying only a single test with a short isolation duration. Both protocols incurred lower costs than the optimal solutions. The Pareto frontiers analyses in Figure 3.4a-c highlight the complexity of decision-making in the context of MRSA surveillance. A thoughtful approach is needed to consider multiple objectives simultaneously and navigate through the inherent trade-offs. The strategies on and close to the Pareto frontier strike a balance between minimizing the impact on QALYs, reducing costs, and controlling the spread of MRSA. There is no single best solution, and the choice of the ideal MRSA surveillance strategy lies in the decision-maker’s priorities. For instance, policymakers may weigh the number of colonizations more given that it is the standard performance metric considered in the infection control community. On the other hand, QALY loss may be important for taking the patient’s perspective (e.g., their discomfort during the process) into consideration. Thus, a future analysis of protocols better balancing these two measures could be of interest.

3.5 Sensitivity Analysis

Our model parameters, such as those related to disease aggressiveness, test sensitivities, and costs, may vary based on the considered region, healthcare setting, followed protocols, and hospital size as reported in the literature (Roth et al. 2016b, Bächli et al. 2022). Therefore, we need to carefully analyze the impact of the changes in model parameters

on the optimal solution. To achieve this, we first conduct a one-way sensitivity analysis to explore the basic behaviour of the optimal protocols and then perform a multi-way sensitivity analysis to collectively assess the key model parameters.

3.5.1 One-way Sensitivity Analysis

3.5.1.1 Disutility Parameters

We derived the disutility parameters by synthesizing data from multiple studies; thus, we conducted a detailed sensitivity analysis on these parameters. For this purpose, we run our model with disutility values ranging between -75% to 75% of the base case estimates with 25% increments. As isolation disutility changes (See Table 3.6), the optimal testing protocol with the first objective function adjusts the testing times and isolation duration to minimize the loss of QALYs. A decrease in isolation disutility leads to the optimal protocol prompting more tests and longer isolation periods for exposed roommates. These changes increase the testing and isolation costs as well as the number of MRSA transmissions during isolation. However, it also increases test accuracy and the number of detected MRSA cases, thus eventually, reducing the total number of colonizations.

As the testing disutility increases, the optimal testing protocol involves less frequent testing and delays the timing of the remaining test to increase test accuracy while limiting the increase in the number of missed cases and transmissions during isolation. Since increasing testing disutility forces optimal strategies to terminate isolation after the first test, both testing and isolation costs decrease. The performance of the optimal strategy

Table 3.6: Comparison of the optimal solutions for minimizing loss of QALYs based on varying isolation, testing, and decolonization and infection disutilities.

Performance measures	-75%	-50%	-25%	Base case	25%	50%	75%
Isolation Disutilities							
Number of exposed roommates	51.29	51.33	51.69	51.83	52.19	52.62	53.01
Number of MRSA colonizations	4.09	4.08	4.05	4.05	4.07	4.10	4.12
Transmissions during isolation	0.25	0.24	0.18	0.18	0.17	0.16	0.16
True positives at the first testing	2.60	2.61	2.47	2.45	2.42	2.41	2.38
True positives at the second testing	0.78	0.71	0.17	0.16	0.11	0.04	0
Number of missed cases	0.70	0.76	1.41	1.44	1.54	1.65	1.74
Number of false positives	2.31	2.32	1.45	1.46	1.39	1.28	1.22
Testing cost	\$4,066	\$4,069	\$2,587	\$2,594	\$2,474	\$2,299	\$2,200
Isolation cost	\$23,948	\$21,842	\$15,943	\$15,383	\$14,375	\$13,552	\$12,761
Total cost	\$33,399	\$31,284	\$23,859	\$23,314	\$22,209	\$21,245	\$20,386
Testing Disutilities							
Number of exposed roommates	51.72	51.72	51.54	51.83	52	52	52
Number of MRSA colonizations	4.02	4.02	4.05	4.05	4.08	4.08	4.08
Transmissions during isolation	0.15	0.15	0.19	0.18	0.19	0.19	0.19
True positives at the first testing	2.23	2.23	2.41	2.45	2.50	2.50	2.50
True positives at the second testing	0.73	0.73	0.72	0.16	0	0	0
Number of missed cases	1.06	1.06	0.91	1.44	1.58	1.58	1.58
Number of false positives	2.34	2.34	2.33	1.46	1.20	1.20	1.20
Testing cost	\$4,126	\$4,126	\$4,099	\$2,594	\$2,154	\$2,154	\$2,154
Isolation cost	\$16,034	\$16,034	\$18,514	\$15,383	\$15,159	\$15,159	\$15,159
Total cost	\$25,455	\$25,455	\$27,942	\$23,314	\$22,678	\$22,678	\$22,678
Decolonization and Infection Disutilities							
Number of exposed roommates	59.25	53.12	52.46	51.83	51.46	51.34	51.33
Number of MRSA colonizations	4.43	4.12	4.09	4.05	4.05	4.08	4.08
Transmissions during isolation	0	0.15	0.17	0.18	0.20	0.24	0.24
True positives at the first testing	1.54	2.34	2.45	2.45	2.44	2.58	2.61
True positives at the second testing	0	0	0	0.16	0.74	0.72	0.71
Number of missed cases	2.89	1.78	1.65	1.44	0.87	0.78	0.76
Number of false positives	1.37	1.22	1.21	1.46	2.33	2.32	2.32
Testing cost	\$2,455	\$2,201	\$2,173	\$2,594	\$4,091	\$4,071	\$4,069
Isolation cost	\$2,825	\$12,393	\$13,995	\$15,383	\$19,282	\$21,472	\$21,842
Total cost	\$11,114	\$20,021	\$21,558	\$23,314	\$28,703	\$30,910	\$31,284

stabilizes when testing disutility increases beyond 25% and decreases beyond 50% of the base case.

Finally, as the decolonization and infection disutilities increase preventing colonizations and missed cases becomes more important for minimizing QALY losses. Thus, the optimal testing protocols recommend more frequent testing and prolonged isolation to increase test accuracy. For lower disutility values of decolonization and infection, the optimal testing strategy is to perform only one test and end isolation quickly. This leads to fewer detected cases, more missed cases, and a higher cumulative number of MRSA cases. In this scenario, the disutilities associated with isolation and testing outweigh those related to colonization and infection.

3.5.1.2 MRSA Transmission Parameters

The prevalence and transmission probability are critical factors affecting MRSA transmission among exposed roommates and thus the optimal testing decisions. We explore three scenarios representing low, medium, and high-risk (i.e., disease aggressiveness) settings when conducting sensitivity analysis. Table 3.7 presents the performance of the optimal strategies for minimizing the loss of QALYs and the number of colonizations across a range of prevalence and transmission probability values derived from the literature.

For the objective of minimizing QALY losses, when the disease aggressiveness is low, transmission risk is minimal. Therefore, a longer isolation duration and only one test after an extended isolation duration are sufficient to control the MRSA propagation and minimize QALY losses. However, as the disease aggressiveness increases more exposed roommates and thus a higher number of MRSA colonizations among them appear. Thus, the optimal strategy employs more tests and extends the isolation duration. Early testing

Table 3.7: Comparison of the optimal solutions based on varying prevalence values and transmission-in-isolation probabilities.

Performance measures	$\rho=0.057^1$ & $\underline{p}=0.0041^2$	$\rho=0.0748^2$ & $\underline{p}=0.0084^2$	$\rho=0.126^3$ & $\underline{p}=0.0149^2$
Minimizing Expected Loss of QALYs			
Number of exposed roommates	50.49	51.83	55.52
Number of MRSA colonizations	2.94	4.05	7.64
Transmissions during isolation	0.06	0.18	0.64
True positives at the first testing	1.80	2.45	4.43
True positives at the second testing	0	0.16	1.63
Number of missed cases	1.15	1.44	1.58
Number of false positives	1.19	1.46	2.35
Testing cost	\$2,092	\$2,594	\$4,342
Isolation cost	\$13,739	\$15,383	\$22,981
Total cost	\$19,704	\$23,314	\$37,375
Minimizing Expected Number of MRSA Colonizations			
Number of exposed roommates	50.53	52.54	57.45
Number of MRSA colonizations	2.92	4.02	7.50
Transmissions during isolation	0.04	0.09	0.27
True positives at the first testing	1.43	1.93	3.50
True positives at the second testing	0.48	0.67	1.24
Number of missed cases	1	1.43	2.76
Number of false positives	2.29	2.34	2.41
Testing cost	\$3,978	\$4,129	\$4,451
Isolation cost	\$11,729	\$11,691	\$12,224
Total cost	\$19,546	\$21,115	\$26,554

¹ Williams et al. (2017)

² Lin et al. (2023)

³ Moore et al. (2008)

is prioritized to promptly detect and separate pre-isolation transmissions, thereby mitigating the risk of secondary (in-isolation) transmissions. Given the increasing contribution of missed cases to new index MRSA cases as disease aggressiveness increases, accurate detection of colonized cases becomes crucial. Consequently, a second test is done after an extended isolation duration to further enhance accuracy. This eventually increases both the treatment and isolation costs. The optimal strategy for minimizing the number of colonizations remains relatively stable as disease aggressiveness increases compared to the one for minimizing QALY losses. That is the optimal strategy includes two tests with shorter iso-

lation durations. As disease transmission probability and prevalence increase, the optimal strategy recommends the same number of tests with shorter follow-up durations.

3.5.1.3 Test Sensitivity

We model time-varying test sensitivities by assuming a constant test sensitivity and incorporating the transition probability from the undetectable to the detectable stage. We investigate the impact of varying constant PCR sensitivity, with a base case value of 80.6%, ranging from 60% to 100%. The changes in test sensitivity necessitate adjustments in testing frequency to balance the benefits of detecting MRSA cases against the associated harms including test disutility, prolonged isolation, and false positive results. As test sensitivity increases, the optimal strategies for both objective functions tend to recommend fewer tests earlier in the isolation. Therefore, increasing test sensitivity reduces the number of MRSA colonizations, missed cases, and exposed roommates. This also leads to a decrease in all cost categories, highlighting the economic benefits of employing more accurate testing methods.

3.5.2 Multi-way Sensitivity Analysis

Section [3.5.1](#) shows that transmission probability and test sensitivity significantly affect the optimal testing protocols and their performances, especially regarding the number of MRSA colonizations. A multi-way sensitivity analysis of these parameters is warranted to specify under what parameter scenarios, there is a significant gap between the optimal strategies and current guidelines/practices and to what degree practical MRSA surveillance

Table 3.8: Comparison of the optimal solutions based on varying test sensitivities.

Performance measures	60%	70%	Base case (80%)	90%	100%
Minimizing Expected Loss of QALYs					
Number of exposed roommates	53.99	52.8	51.83	51.14	50.34
Number of MRSA colonizations	4.21	4.11	4.05	4.01	3.95
Transmissions during isolation	0.17	0.16	0.18	0.18	0.18
True positives at the first testing	1.74	1.98	2.45	2.74	3.01
True positives at the second testing	0.91	0.85	0.16	0	0
Number of missed cases	1.56	1.28	1.44	1.26	0.94
Number of false positives	2.45	2.39	1.46	1.18	1.16
Testing cost	\$4,330	\$4,223	\$2,594	\$2,119	\$2,086
Isolation cost	\$16,689	\$16,353	\$15,383	\$14,938	\$14,916
Total cost	\$26,560	\$25,991	\$23,314	\$22,333	\$22,200
Minimizing MRSA Colonizations					
Number of exposed roommates	54.93	53.68	52.54	51.65	50.64
Number of MRSA cases	4.21	4.11	4.02	3.95	3.91
Colonized cases before isolation	4.11	4.02	3.93	3.86	3.79
Transmissions during isolation	0.10	0.10	0.09	0.09	0.12
True positives at the first testing	1.50	1.71	1.93	2.12	2.68
True positives at the second testing	0.81	0.77	0.67	0.54	0.06
Number of missed cases	1.89	1.63	1.43	1.29	1.16
Number of false positives	2.44	2.39	2.34	2.30	1.45
Testing cost	\$4,328	\$4,229	\$4,129	\$4,051	\$2,577
Isolation cost	\$12,256	\$11,962	\$11,691	\$11,479	\$11,797
Total cost	\$22,127	\$21,605	\$21,115	\$20,731	\$19,516

strategies may help cover this gap. Figure 3.5 illustrates the potential reduction in MRSA colonizations achieved by the current practice (Cult0+PCR3), the ideal practical strategy (PCR0+PCR2), and the optimal strategy for minimizing the number of colonizations compared to the guideline based on changes in transmission probability, culture sensitivity, and PCR sensitivity values. For instance, when the transmission probability is 4.8%, and the sensitivities of conventional culture and PCR tests are 53% and 96% respectively, the Cult0+PCR3, PCR0+PCR2, and the optimal strategy prevent 1.09, 1.58, and 1.96 more MRSA colonizations compared to the Cult0+Cult6, respectively. In the heat maps

of Figure 3.5, the darker areas represent a more significant reduction in the number of colonizations.

Figure 3.5 shows that Cult0+PCR3 can reduce the number of MRSA colonizations compared to the current guidelines unless the sensitivity of the culture test is higher than PCR sensitivity and transmission risk is very low. This reduction can be achieved even if the culture test sensitivity is higher than that of PCR when the disease transmission probability is high enough. Instances, where Cult0+Cult6 outperforms Cult0+PCR3, are relatively rare, and associated parameter combinations are generally unlikely given that PCR is known to be a more accurate test (PIDAC 2013). When Cult0+PCR3 does not achieve a lower number of MRSA colonizations than Cult0+Cult6, the difference is negligible, less than 0.3.

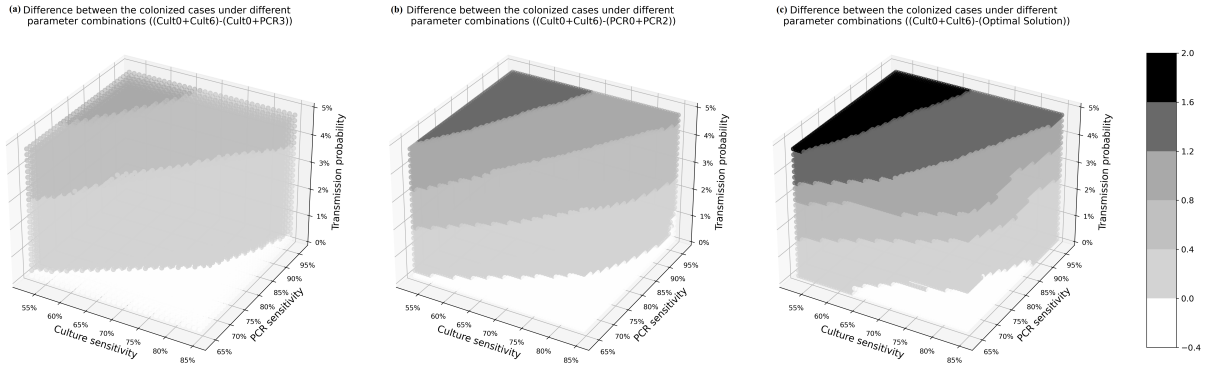


Figure 3.5: Difference between the number of MRSA colonization under considered surveillance testing protocol for different combinations of transmission probabilities and sensitivity levels.

A comparison of the heat maps in Figures 5a and 5c illustrates the optimality gaps associated with the guidelines and current practices. As the transmission probability increases the reduction in the number of colonizations compared to the guidelines increases

significantly. In addition, we observe a very small area of parameter combinations for which Cult0+Cult6 performs better than the optimal strategy. As the optimal strategy only considers PCR testing, the guidelines may perform better when disease aggressiveness is very low and the culture test is way more accurate than the PCR test (an extremely unlikely scenario). The current practice, Cult0+PCR3, covers this optimality gap reasonably when disease aggressiveness is low. However, Cult0+PCR3 is less effective in covering this gap for medium and high disease aggressiveness, which may represent the Canadian setting in remoter locations and U.S. settings where MRSA risk is higher compared to Ontario, Canada.

Although the current practice leaves some optimality gaps, this can be covered reasonably well by alternative practical strategies. Figure 5b shows that PCR0+PCR2 closely mirrors the heat map patterns for the optimal solution with a slightly lower reduction in the number of colonizations. Therefore, it covers the optimality gap much better when the disease aggressiveness is medium and high. The good performance of PCR0+PCR2 for realistic parameter combinations implies that a PCR-based MRSA surveillance strategy can safely replace the current culture-based surveillance practices. The detailed comparison in Table 3.5 and the heat map in Figure 5b demonstrates that health outcomes can be significantly improved in a cost-saving manner by replacing the culture test with PCR for the surveillance of the exposed roommates.

3.6 Conclusions

Guidelines for MRSA prevention and control recommend surveillance testing and contact isolation measures for roommates who have been in contact with an index MRSA case(s) in hospitals and other healthcare institutions. To this end, several controversial questions about MRSA surveillance are being discussed: should PCR testing replace conventional culture testing to reduce isolation, is day 0 testing cost-effective, or what is the best timing for initial and follow-up testing of contacts post-exposure ([Evison and Mühlemann 2008](#), [Ng et al. 2012](#), [Lin et al. 2023](#)). Given the scarcity of reliable published data due to variabilities in surveillance practices, health care systems and incidence rates, mathematical models are needed to address these important policy questions and determine the best strategies for the post-exposure surveillance of roommates. However, developing analytical models for such an infectious disease has several challenges. The models need to explicitly incorporate the effects of the following factors on disease spread and optimal selection of interventions: *i*) partial information from testing, *ii*) time-dependent test sensitivities due to increasing bacteria load over time, *iii*) dynamically changing room settings, and *iv*) missed cases (surveillance false negatives). A partially observable modeling framework is needed to address all these issues, and such models are known to be hard to solve. The proposed model addresses all these challenges efficiently via novel disease and model state definitions within an MDP framework facilitating the exact solution to the problem.

By modeling MRSA progression through transitions from undetectable MRSA to detectable MRSA states, the proposed model captures time-varying test sensitivities in a

simple but effective manner using only a few model parameters. Once the disease propagation in a single room is modeled as a hidden Markov model, we capture the transmission in a hospital by defining an MDP model that tracks sufficient statistics, i.e., the timing of each test and the number of resulting positive cases. This state space definition enables us to convert the considered partially observable problem into an equivalent MDP by calculating the probability of each patient being in each core health state (i.e., belief states) through a series of Bayesian updates, starting from the initial disease prevalence on day 0. Thus, this hospital-level state definition explicitly incorporates partial observability of health states, imperfect testing, and room setting changes into the model and facilitates the efficient solution of the model. The novelty of this model definition is particularly noteworthy because, unlike in classical POMDPs, the complexity of hospital-level state definition does not exponentially increase with the number of core health states. That is the proposed model remains tractable even with a large number of core health states given that the tests yield only a positive or negative result. The effect of missed cases is also captured by the additional factors included in the hospital-level state definitions. The proposed model incorporates these important infection dynamics while maintaining computational tractability by considering a limited number of surveillance tests and missed case risk clusters. Limiting the number of considered surveillance tests is in line with the current practices. Clustering missed cases into risk clusters is also reasonable, as several missed case combinations lead to very similar risk values, and the effects of small fluctuations in the missed case risks on the total number of MRSA colonizations are limited. Furthermore, the proposed model is generalized in terms of the number of considered tests and risk clusters.

The idea of keeping track of sufficient statistics to capture partial observability has been successfully applied in various OR applications, particularly in supply chain settings, e.g., the time until the next inventory replenishment is used to derive demand distribution (Wang and Zhang 2021). Earlier attempts to apply this approach to disease testing also exist (Kırkızlar et al. 2010); however, these approaches either do not account for the spread or propagation of a disease over a population or assume perfect test performance. Therefore, the proposed novel MDP model is the first analytical model to analyze optimal testing decisions for an infectious disease, considering disease propagation among susceptible individuals in a hospital setting. Using this model, we analyzed the surveillance of hospital-acquired infections, focusing on the surveillance of exposed roommates of index MRSA cases. We determined the optimal testing schedule and resulting isolation duration considering objective functions of minimizing the total expected loss of QALYs and the expected number of MRSA colonization. We optimally solved the model using data from the literature and conducted several analyses. Additionally, we compared the optimal solution with current guidelines and practical testing protocols similar to these guidelines. Thanks to our analytical model, we were able to compare these protocols through detailed multi-way sensitivity analyses, which would take months to complete using conventional simulation packages. These numerical analyses provide valuable insights for clinicians to improve MRSA and possible other AROs surveillance practices.

The optimal surveillance strategy derived from the MDP model recommends varying the number of tests and their timing based on several factors, including the number of isolated rooms, the bed number of these rooms, and initial test outcomes, for both objective functions. By varying testing decisions according to these factors, the model balances the

risks of further transmission (in isolation and due to missed cases) while limiting the cost and disutility of prolonged patient isolation. In the end, the optimal testing strategies for both objective functions reduce the number of MRSA acquisitions by mitigating transmission risk and improving patients' well-being by decreasing the isolation duration. Despite incurring higher testing costs, the optimal strategies significantly reduce isolation costs, and thus, the total cost. Consequently, these optimal testing decisions provide substantial cost savings and improvements in health outcomes compared to current practices. For instance, we observed reductions of up to 3.4% in MRSA colonizations, up to 36.3% in total costs, and up to 18.9% in the loss of QALYs compared to current practices. Although implementing these optimal testing decisions may pose challenges for practical application due to their complexity (i.e., actions vary dynamically over time), they offer valuable insights for enhancing current practices by highlighting potential areas for improvement.

We obtained the following practical insights from our numerical experiments. First, the ideal surveillance strategy may involve applying different testing times to semi-private and cohort room cases given their differing transmission dynamics and risks from the remaining exposed roommates. In the latter, the risk of transmission during isolation is significant, initiating testing at an earlier phase is crucial for identifying asymptomatic patients who may have acquired the disease (from the initial case), thereby preventing further spread. In contrast, a less aggressive strategy can be applied to semi-private rooms. Second, when there are multiple rooms in isolation, more patients are at risk but also because the likelihood of a missing case is increased. Therefore, delaying initial and follow-up testing to increase test sensitivities by improving detection rates is more valuable than ending isolation early to save costs and limit the in-isolation transmissions. Third, although

optimal solutions vary based on room settings and objective function, a common aspect emerges that guides decision-makers towards reducing MRSA colonizations and improving other metrics: more frequent tests and shorter isolation periods. Fourth, our comparison of the optimal protocol with the current guidelines (See Figure 3.5) indicates that replacing culture-based surveillance with PCR-based surveillance would be effective in improving health outcomes and cost-saving unless the disease transmission probability is very low while culture sensitivity is significantly higher than PCR sensitivity – a scenario that is not very likely. This insight also aligns well with the findings of several earlier studies (Ng et al. 2012, Lin et al. 2023). Fifth, contrary to the claims made by some earlier studies, our results imply that day 0 testing might be effective in interrupting the transmission chain during isolation. For example, our comparison in Figure 3.4 shows that many Pareto-frontier strategies, which are close-to-optimum for minimizing the number of colonizations, employed initial testing at day 0, such as PCR0+PCR2.

Our analyses in Figure 3.4 show that among the various protocols, the surveillance strategy of PCR0+PCR2 closely aligns with the performance of the optimal solution in achieving the lowest number of MRSA colonization. For minimizing the loss of QALYs, on the other hand, PCR3 performs close to the optimal solution. These results imply that by adjusting the timing of the initial and follow-up tests and switching from culture to PCR testing (i.e., following the third and fourth insights above), the performance of the guidelines or current practices can be improved to a level close to the optimal solution for specific objective functions. For example, the Pareto-frontier analysis indicates that by perturbing the currently practiced surveillance protocol of Cult0+PCR3 by replacing the day 0 test with a PCR and applying the follow-up test a day earlier (i.e., PCR0+PCR2),

both the number of MRSA cases and QALYs loss can be reduced compared to the reference guidelines. Although PCR0+ PCR2 performs close to optimal in one performance metric, there remains an optimality gap compared to other metrics. Due to the complex trade-off dynamics, none of the simple practical strategies that follow the same structure as the current guidelines may perform close to optimal in all metrics. However, by applying different simple strategies to different room types or room combinations, this remaining gap could be addressed. This is left for future research.

This has several practical implications for setting IPAC policies for MRSA control programs within hospitals, especially in facilities with insufficient private rooms or at overcapacity. By viewing the modelling results as setting ranges of transmission outcomes based on real world variables (test number, frequency, modality and possibly organism) one can take reassurances that reducing the isolation time benefits both the patient and organization's bed flow. It also supports the financial case for strategic investment in diagnostic services to support algorithms that wish to shorten the time between surveillance testing without compromising on case detection. Given that isolation requirements represent a significant cost and burden, safely reducing their unnecessary use is important given the increasing of AROs competing for these resources.

Our results demonstrate the effectiveness of our MDP modeling framework in identifying optimal MRSA surveillance strategies and providing guidance on improving current practices. It is worth noting that infection prevention and control guidelines recommend similar approaches for contacts of patients infected or colonized with Vancomycin-resistant enterococci (VRE), Carbapenemase-producing organisms (CPO) and *Candida auris* (*C. auris*) ([PIDAC 2013](#), [PHO 2023](#)). The proposed model is directly applicable to these

diseases as well especially given the reliance and performance on conventional cultures for surveillance testing. The proposed framework is general enough to be applied to the control and management of such infections that require the isolation of patients in groups, such as COVID-19 and tuberculosis. To capture the randomness in propagation and testing results of such diseases, the proposed modeling framework could be quite helpful, either as the primary methodology or as a starting point for the ideal model. In some applications where the population size or the disease’s natural history necessitates a large number of tests or a prolonged isolation duration (e.g., tuberculosis), the scalability of the proposed model may need to be improved through structural analysis of the optimal solution or approximate MDPs. This is also left for future studies. We also assumed that healthcare workers strictly adhere to guidelines, effectively eliminating the risk of transmission from healthcare personnel to patients. While this is a reasonable assumption for the Ontario healthcare system, given the stable hygiene principles in place ([PIDAC 2013](#), [PHO 2023](#)), future research should aim to incorporate the transmission risk posed by healthcare workers into the model to enhance its generalizability.

Chapter 4

An HMM-based Simulation Model for MRSA Surveillance

The US Centers for Disease Control and Prevention (CDC) recommends active surveillance testing to identify asymptomatic MRSA colonization, based on specific risk factors such as antibiotic exposure history, prolonged hospital stays, and contact with other MRSA-colonized patients ([CDC 2006](#)). Similarly, the Ontario Provincial Infectious Diseases Advisory Committee (PIDAC) advises collecting two sets of specimens on different days, with at least one specimen taken a minimum of seven days after the last exposure to an MRSA case ([PIDAC 2013](#)). However, the optimal test modality, timing and interval for active surveillance are not well defined in guidelines. The lack of national guidance on testing strategies complicates decision-making and leads to controversy, as these factors can significantly impact both costs and health outcomes. Surveillance measures, including testing and isolation, are resource-intensive and costly to implement.

Despite being a critical issue in hospitals, studies on surveillance strategies for managing the risk of MRSA transmission among exposed roommates are limited (Ng et al. 2012, Lin et al. 2023). There is a need for studies that address practical challenges in infection control and explicitly evaluate the trade-offs between alternative strategies (Shenoy et al. 2018). Transparent and well-validated simulation models can play a critical role in this regard by providing insights into potential surveillance testing protocol options. Such models facilitate the evaluation of competing surveillance protocols and support evidence-based decision-making, guiding hospitals in selecting the most effective and efficient surveillance strategies.

The MDP model proposed in Chapter 3 provides an analytical framework to optimize MRSA testing protocols and identify the gap between optimal solutions and practical testing practices. While the MDP model can efficiently analyze the problems in small and medium-sized hospitals, its scalability could be limited when applied to larger institutions due to the increased number of rooms and the complexity of capturing varying effects of missed cases. To address this scalability issue, it is essential to develop a model capable of handling larger hospital settings efficiently and apply the lessons learned from the analytical MDP model to more general problem settings. As hospital size increases, it becomes crucial to explicitly model the effects of missed cases on MRSA progression and transmission, as clustering methods may not sufficiently account for the varying impact of missed cases. Additionally, solving this problem fast is critical due to the significant variability in disease progression across different healthcare settings. Factors such as disease aggressiveness, prevalence, and transmission risk can vary greatly, requiring rapid analyses to adapt testing protocols to specific institutional characteristics and very detailed

multi-way sensitivity analyses of various parameter settings to determine under what conditions specific protocols outperform current practices or alternative strategies. Identifying parameter thresholds beyond which a particular testing strategy is more effective is essential for informed decision-making. To meet the requirements of scalability, granularity in capturing missed cases, and computational efficiency, we propose a Hidden Markov Model (HMM)-based simulation model. The proposed model can evaluate the effectiveness of MRSA testing protocols for exposed roommates of index MRSA patients and specify ideal surveillance strategies in diverse healthcare settings by relaxing the limitations on hospital size, room numbers, and missed case representation.

The remainder of this chapter is organized as follows. The next section reviews the literature on simulation studies related to MRSA. In Section 4.2, the HMM-DES framework is described. Section 4.3 presents a comprehensive analysis to evaluate the performance of various MRSA testing protocols and address key controversial questions regarding MRSA surveillance testing. Finally, Section 4.4 provides concluding remarks.

4.1 Literature Review

Numerous studies in the infectious disease testing literature employ simulation models, compartmental models, and various analytical approaches (Rais and Viana 2011, Silal 2021). The relevant literature on optimizing testing decisions for infectious diseases using analytical models has already been reviewed in Section 3.2.

Simulation modeling is increasingly utilized to enhance understanding of the epidemi-

ological patterns of healthcare-associated infections and to support decision-making in infection prevention and control ([Nguyen et al. 2020](#)). Combining two different simulation or modeling techniques (i.e., hybrid models) can help solve different aspects of the problem. Hybrid simulations have been used in many applications, including supply chain, transportation and logistics, and healthcare. Existing review articles report hybrid simulation models applied to various application domains ([Brailsford et al. 2019](#), [dos Santos et al. 2020](#), [Kar et al. 2024](#)).

The combination of OR models is extensively discussed in the literature, as each model type offers distinct strengths and limitations. Integrating different methods helps overcome the drawbacks associated with relying on a single approach ([Brailsford et al. 2019](#)). The integration of Markov models with simulation models has been utilized in several previous studies to model the natural history of diseases, particularly for chronic conditions ([Roberts 1992](#), [Alagoz et al. 2005](#), [McClean et al. 2011](#), [Tejada et al. 2015](#), [Meester et al. 2018](#)). Our work further demonstrates the effectiveness of this approach.

MRSA is one of the most prevalent pathogens studied in simulation models for healthcare-associated infections due to its significant contribution to high morbidity and mortality rates, often leading to severe complications such as sepsis ([van Kleef et al. 2013](#), [Kourtis et al. 2019](#)). The transmission and propagation of MRSA in healthcare settings have been extensively studied by both the mathematical modeling and epidemiological communities. Numerous studies focus on understanding the epidemiological characteristics of MRSA and estimating key disease parameters, such as prevalence and transmission rates, using statistical models applied to hospital data ([Sampathkumar 2007](#), [Tübbicke et al. 2012a,b](#), [Kourtis et al. 2019](#)). Additionally, many studies have employed models to evaluate the

effectiveness of infection control interventions, including hand hygiene, contact isolation and decolonization to control the MRSA spread in healthcare facilities ([Barnes et al. 2010](#), [van Kleef et al. 2013](#), [Shenoy et al. 2018](#), [Barnes et al. 2020](#)).

Most existing studies on MRSA testing have focused on analyzing the cost and clinical effectiveness of universal and targeted admission screening for primary MRSA case detection. These studies typically rely on secondary data, decision trees, or computer simulations ([Hubben et al. 2011](#), [Leonhardt et al. 2011](#), [Deeny et al. 2013](#), [McKinnell et al. 2015](#), [Goldsack et al. 2016](#), [Roth et al. 2016b,a](#)). While the emphasis has been primarily on admission screening, there has been limited research addressing MRSA control and management strategies for exposed roommates. Only a few studies have used secondary institutional data to estimate MRSA incidence among exposed roommates under different surveillance strategies ([Moore et al. 2008](#), [Ng et al. 2012](#), [Williams et al. 2017](#), [Bächli et al. 2022](#)).

The work most similar to ours is that of [Lin et al. \(2023\)](#), where a stochastic discrete-event simulation model is developed to evaluate and compare the performance of conventional culture and direct PCR testing strategies among roommates exposed to index MRSA cases in Canadian community hospitals. However, our proposed HMM-based simulation model differs from their approach in several key aspects. First, our model integrates an HMM with a simulation, where MRSA progression and transmission dynamics within isolated rooms are captured by the HMM. This analytical approach allows us to model disease dynamics at the room level with a limited number of random number generations, significantly enhancing computational efficiency, particularly for large institutions. Additionally, the HMM’s state definitions allow us to account for varying test sensitivities of culture and

PCR tests overtime, facilitating the evaluation of diverse testing protocols (i.e., testing can be done at any time point rather than focusing only at day 0, day 3 and day 6 testing). Lastly, this hybrid framework allows us to address several controversial policy questions related to MRSA surveillance testing, offering insights into the trade-offs and effectiveness of various testing strategies, which are not explored in [Lin et al. \(2023\)](#).

4.2 Simulation Model

We propose a discrete-event simulation (DES) model integrated with a Hidden Markov Model (HMM). The HMM-DES framework captures stochastic elements, such as random arrivals, and incorporates decision-making processes related to testing, while modeling the disease progression and transmission dynamics among exposed roommates. The DES component simulates the implementation of alternative testing protocols for roommates in isolated rooms and reports key performance metrics, while the analytical HMM proposed in the previous chapter models MRSA transmission and progression within each isolated room under a particular testing protocol.

In [Section 3.3.1](#) we describe the transmission and progression dynamics for a single patient in a multi-bedded room. Patient health states are defined as non-colonized, colonized-undetectable, and colonized-detectable. Defining two different health states for colonized cases enables the incorporation of varying testing sensitivities across different days. The state of the HMM represent the number of exposed roommates in each MRSA status. We refer the readers to [Section 3.3.2](#) for the details on the initial probability distribution over states, transmission and observation probabilities.

In the HMM-DES framework, the disease progression and transmission probability distributions for each isolation day are derived from an analytical model under given test results, and room type arrivals. These distributions are utilized to calculate the core state probabilities at each period and the performance metrics associated with them during the whole isolation period. Therefore, by generating only a limited number of random numbers to simulate test results (observations) and room type arrivals, the MRSA progression and transmission in a given set of rooms can be simulated for the entire isolation duration. In contrast, a classical simulation model would require random number generation for each day’s progression, transmission, test results, and for each patient. These random variates would then be used to derive the performance metrics, resulting in significantly higher computational demand. Therefore, the proposed HMM-DES model achieves significantly improved computational efficiency compared to the simulation model developed for exposed roommate surveillance in [Lin et al. \(2023\)](#). This enhanced efficiency allows the proposed model to address a broader range of policy questions, identifying the ideal surveillance protocols for different parameter settings through a much more comprehensive sensitivity analysis, i.e., parameter thresholds for considered alternative protocols are derived with much greater precision.

Our simulation model is based on guidelines that recommend isolating and conducting surveillance testing for roommates exposed to index MRSA cases, involving the collection of two specimens post-exposure. Figure [4.1](#) provides an illustration of the simulation process flow. We use the following performance metrics for the comparison of alternative testing protocols: the number of MRSA cases, colonized cases before and during isolation, missed cases, false positives, and the total cost, including expenses related to testing, isolation,

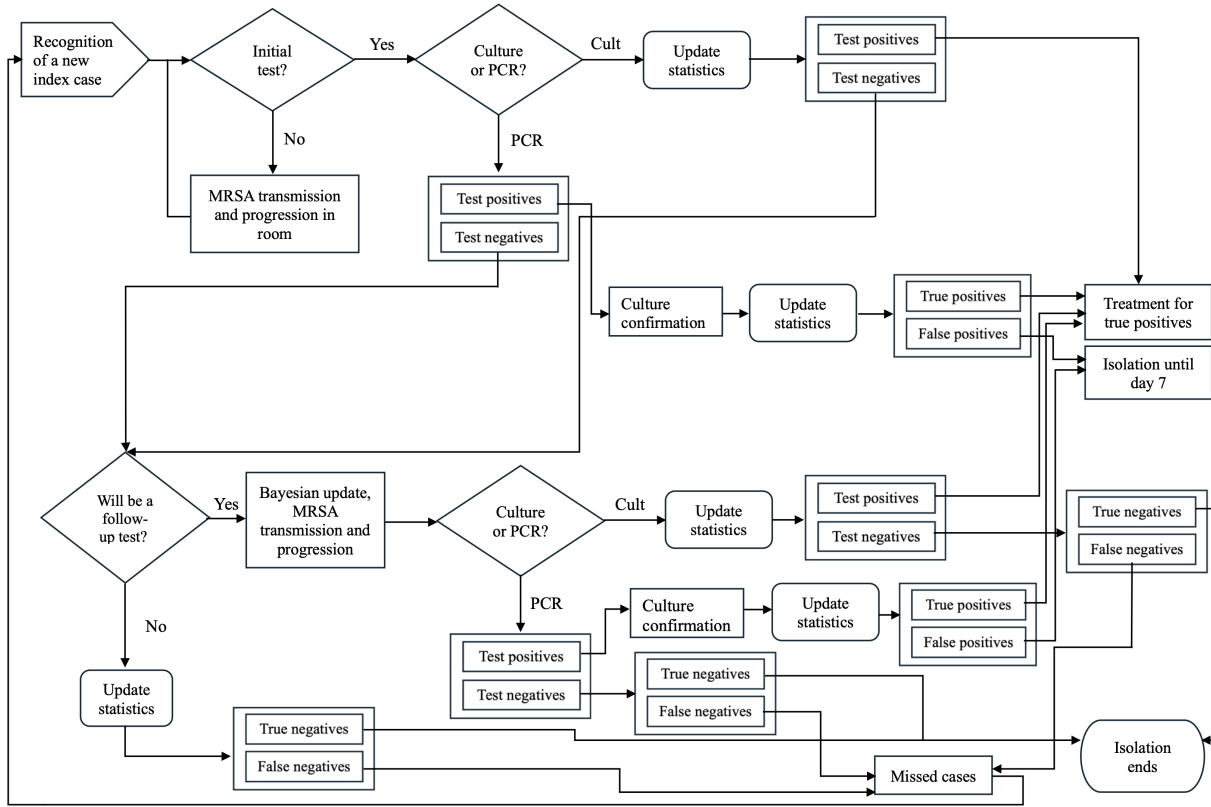


Figure 4.1: Simulation flow chart.

In the figure, test positives and test negatives refer to roommates with positive and negative test results, respectively. True positives are colonized roommates correctly identified as colonized, false positives are noncolonized roommates incorrectly identified as colonized, true negatives are noncolonized roommates correctly identified as noncolonized, and false negatives are colonized roommates incorrectly identified as noncolonized.

MRSA colonization, and the loss of quality-adjusted life years.

Once an index MRSA case is recognized in a multi-bedded room, the patient is removed from the room for the treatment and the roommates are placed in contact isolation and undergo surveillance testing. The room type is determined based on a predefined distribution, and the start time of isolation for each room is recorded. Based on the prevalence and

detectability on post-exposure day 0, the initial probability distributions over states are determined. Until the initial test is conducted, patients may transition between different health states, which is modeled and managed by the HMM. For PCR-based surveillance protocols, positive results must be confirmed with a culture test ([PIDAC 2013](#)). Following the initial test, the relevant statistics are updated. For protocols involving only a single test, the process concludes at this stage. True positives are transferred for treatment, while patients with a positive PCR test but a negative culture confirmation (false positives) remain in isolation until day 7, with a follow-up culture test on day 6. For protocols with a follow-up test, patients with negative initial test results remain in isolation. The probability distribution for their health states is updated using Bayesian inference based on the initial test results. During the period between the initial and follow-up tests, disease transmission and progression may occur for these patients which are handled by the HMM. Once the second test results are available, true positives are moved to a positive room for treatment. False positives continue isolation until day 7. At the end of isolation, patients with negative test results are safely released. However, false negatives (missed cases) may lead to additional contacts, increasing the rate of recognizing a new index MRSA case. For each room, test results and associated statistics are calculated and updated. The annual performance metrics for the hospital are then reported based on these evaluations.

The simulation model is coded in Java. We conduct 10,000 simulation replications for each surveillance strategy, with each replication representing one year. We calculate annual performance metrics resulting from each surveillance testing protocol. The validation of the conceptual model was conducted through an iterative and consultative process with Dr. William Ciccotelli. Additionally, the model was validated by using the same data and

comparing the performance of the Cult0+Cult6 testing protocol with results from the published work by [Lin et al. \(2023\)](#).

4.3 Computational Experiments

This section presents numerical analyses for evaluating the performances of MRSA surveillance testing protocols recommended by guidelines, clinicians, and other possible practical surveillance options. The model is applied to Grand River Hospital 400-bed community acute care hospital, utilizing data from the hospital’s Infection Prevention and Control (IPAC) department and relevant literature. We consider multiple room types, including semi-private rooms (2-bedded), cohort rooms (4-bedded), and ward rooms. Ward rooms represent a scenario where the index case initially stays in a semi-private room (exposing one roommate) and is later transferred to a cohort room due to a longer length of stay (exposing three additional roommates), resulting in a total of four exposed roommates.

4.3.1 Evaluating Testing Protocols: Trade-offs, Controversies, and Performance Improvements in the Base-case Scenario

MRSA testing protocols involve several key decisions, including the choice of testing method, the timing of tests, and the interval between them. Testing typically begins as soon as exposure is identified, and follow-up testing may be conducted to account for delayed colonization. Some guidelines recommend additional testing from other body sites or routine follow-ups to ensure comprehensive monitoring, though practices vary across

institutions, reflecting ongoing debate about the most effective strategies.

In Canada, the most common guideline-supported practice involves culture tests on post-exposure day 0 and day 6 (Cult0+Cult6). Another approach, currently implemented at Grand River Hospital, includes an initial culture test on day 0 followed by a PCR test on day 3 (Cult0+PCR3). Our first analysis in the next section compares these two current practices.

Protocols can involve various combinations, such as a single PCR test, two PCR tests on different days, or a mix of culture and PCR tests, with the culture collected on one day and the PCR on another. We evaluate these alternative protocols and compare them with current practices to determine whether they lead to improvements and to what extent these improvements can be achieved. Using the proposed simulation model, we explore and address several controversial questions related to MRSA testing protocols in the following sections:

- What is the ideal timing for a follow-up test after the initial day 0 culture test?
- Is the day 0 culture test effective, or should it be removed?
- Can the day 0 culture test be replaced with a PCR test on day 0?
- Are two tests necessary, or is a single test sufficient?
- What is the ideal timing for conducting two PCR tests or two culture tests?
- Can the culture-based surveillance protocol be effectively replaced with a PCR-based protocol?

4.3.1.1 Guidelines versus Current Practice

Table 4.1 summarizes the base-case performance of post-exposure MRSA surveillance using the Cult0+Cult6 and Cult0+PCR3 strategies. The findings on the clinical and cost-effectiveness of Cult0+PCR3 align with previous studies (Ng et al. 2012, Lin et al. 2023), as well as those reported in 3.4.2.

Table 4.1: Performances of the guideline and current practice for the base-case scenario.

Performance measures	Guideline		Current Practice	
	Cult0+Cult6	95% CI	Cult0+PCR3	95% CI
Number of exposed roommates	300.24	(299.68-300.79)	303.32	(302.75-303.89)
Number of MRSA colonizations	23.93	(23.88-23.97)	23.44	(23.39-23.48)
Transmissions before isolation	22.46	(22.42-22.50)	22.69	(22.65-22.73)
Transmissions during isolation	1.47	(1.46-1.47)	0.75	(0.75-0.75)
True positives at the first testing	6.72	(6.67-6.77)	6.83	(6.77-6.88)
True positives at the second testing	9.70	(9.63-9.76)	8.49	(8.45-8.53)
Number of missed cases	7.25	(7.23-7.26)	7.95	(7.94-7.96)
Number of false positives	0	(0.00-0.00)	6.90	(6.86-6.94)
Testing cost	\$8,157	(\$8,142-8,172)	\$16,383	(\$16,352-16,414)
Isolation cost	\$149,000	(\$148,720-149,280)	\$77,892	(\$77,745-78,039)
MRSA colonization cost	\$31,495	(\$31,436-31,554)	\$30,850	(\$30,792-30,908)
Total cost	\$188,652	—	\$125,126	—
Total loss of QALYs	26.36	(26.31-26.42)	23.20	(23.16-23.24)

CI: Confidence interval

Cult0+PCR3 results in slightly more missed cases, leading to a marginally greater number of exposed roommates. Both protocols result in 23–24 MRSA colonizations, corresponding to a 7.7–7.9% colonization rate among approximately 300 exposed roommates. The majority of MRSA colonizations result from primary transmissions, occurring before isolation and prior to the removal of the index case. Cult0+PCR3 reduces MRSA col-

onizations due to secondary transmissions by 49%, effectively limiting the exposure of roommates to undetected MRSA cases. Overall, Cult0+PCR3 achieves a 2.1% reduction in MRSA cases compared to Cult0+Cult6. Due to the imperfect specificity of the PCR test, Cult0+PCR3 leads to a false positive test result for 6.90 exposed roommates.

Cult0+PCR3 is also more cost-effective due to its shorter isolation duration. Although PCR testing is more expensive and requires confirmatory testing for false positives, which doubles testing costs compared to Cult0+Cult6, the shorter isolation requirements with Cult0+PCR3 leads to a reduction in isolation expenses by more than half. This significant reduction in isolation costs outweighs the increase in testing expenses, leading to a 34% decrease in the overall expected cost with Cult0+PCR3. Our analysis shows that combining a day 0 culture test with a day 3 PCR test achieves health outcomes that are comparable to, if not better than, culture tests conducted on days 0 and 6, while significantly reducing costs.

4.3.1.2 Ideal Timing for Follow-up Testing: Culture versus PCR After Day 0 Culture Test

We investigate the optimal test modality and timing for the follow-up test after the initial culture test on day 0. Table 4.2 provides a performance comparison of testing protocols with follow-up culture and PCR tests on different days, identifying those that result in the minimum number of MRSA colonizations.

Using a PCR test as a follow-up to the initial culture test on day 0 (Cult0+PCR4) results in fewer MRSA colonizations compared to a follow-up culture test (Cult0+Cult3).

Table 4.2: Performance comparison for follow-up tests (Culture vs. PCR) on different days for the base-case scenario.

Performance measures	Cult0+Cult3	Cult0+Cult4	Cult0+PCR3	Cult0+PCR4
Number of exposed roommates	307.81	304.76	303.32	299.16
Number of MRSA cases	23.78	23.79	23.44	23.36
Colonized cases before isolation	23.02	22.80	22.69	22.38
Transmitted cases during isolation	0.76	1.00	0.75	0.98
Detected at the first testing	6.95	6.82	6.83	6.73
Detected at the second testing	7.50	8.47	8.49	9.67
Number of missed cases	9.28	8.37	7.95	6.89
Isolation Cost	\$88,192	\$108,737	\$77,892	\$97,390
Testing Cost	\$8,396	\$8,301	\$16,383	\$16,127
Colonization Treatment Cost	\$31,307	\$31,323	\$30,850	\$30,748
Total Cost	\$127,895	\$148,361	\$125,126	\$144,264
Total Annual Loss of QALY	25.15	25.34	23.20	23.19
Number of false positive cases	0.00	0.00	6.90	6.88

Both testing approaches achieve the minimum number of MRSA colonizations when conducted around the same timeframe (day 3 or day 4). Due to its higher sensitivity, the PCR follow-up test results in fewer MRSA colonizations and a reduced number of missed cases. Although PCR testing incurs higher testing costs, it ultimately reduces overall expenses by decreasing the number of exposed roommates and, consequently, the isolation costs.

Given the advantages of PCR testing in terms of both cost and health outcomes, the follow-up test after day 0 can be replaced with a PCR test. Depending on the decision maker's preference, the PCR follow-up can be conducted on day 3 to achieve cost savings, with only a slight increase in the number of MRSA colonizations.

4.3.1.3 Evaluating Protocols and Alternatives for Day 0 Testing

The benefit of day 0 testing in MRSA surveillance is questioned in the literature. Earlier studies recommended eliminating the day 0 culture test due to its low sensitivity to save laboratory resources (Evison and Mühlemann 2008, Ng et al. 2012). We compare the performance of guidelines and current practices with and without the day 0 culture test, with results presented in Table 4.3. Cult0 is effective in identifying and removing unrecognized

Table 4.3: Performance comparison of the guideline and current practice with and without day 0 culture test for the base-case scenario.

Performance measures	Cult0+Cult6	Cult6	Cult0+PCR3	PCR3
Number of exposed roommates	300.24	310.69	303.32	309.99
Number of MRSA cases	23.93	25.41	23.44	24.28
Colonized cases before isolation	22.46	23.24	22.69	23.19
Transmitted cases during isolation	1.47	2.17	0.75	1.09
Detected at the first testing	6.72	14.99	6.83	14.36
Detected at the second testing	9.70	0.00	8.49	0.00
Number of missed cases	7.25	10.04	7.95	9.73
Isolation Cost	\$149,000	\$156,795	\$77,892	\$80,696
Testing Cost	\$8,157	\$4,232	\$16,383	\$12,736
Colonization Treatment Cost	\$31,495	\$33,445	\$30,850	\$31,960
Total Cost	\$188,652	\$194,472	\$125,126	\$125,391
Total Annual Loss of QALY	26.36	26.82	23.20	22.27
Number of false positive cases	0.00	0.00	6.90	7.09

MRSA cases from isolation rooms, thus reducing the risk of secondary transmissions. Our findings indicate that removing Cult0 and instead applying only Cult6 (PCR3) results in a 47.6% (45.3%) increase in transmissions during isolation and a 6.2% (3.6%) increase in

the total number of MRSA colonizations. Additionally, Cult6-only and PCR3-only testing protocols are associated with 41.2% and 22.4% more missed cases, respectively. While removing Cult0 reduces testing costs by 48.1% for Cult6-only and 22.3% for PCR3-only protocols, the resulting increase in isolation and colonization treatment costs makes these strategies more expensive overall. Our results support the value of day 0 testing for MRSA surveillance, aligning with current guidelines ([PIDAC 2013](#)).

We further assess the impact of removing the Cult0 test by evaluating alternative protocols with optimally timed culture and PCR tests, beyond just Cult6 and PCR3. Table 4.4 highlights the performance of single culture and PCR tests with optimal timing in terms of minimizing the number of MRSA colonization.

Table 4.4: Performance comparison of the current practices and single culture and PCR tests with optimal timing for the base-case scenario.

Performance measures	Cult0+Cult6	Cult3	Cult0+PCR3	PCR2
Number of exposed roommates	300.24	317.60	303.32	314.28
Number of MRSA cases	23.93	24.87	23.44	24.25
Colonized cases before isolation	22.46	23.76	22.69	23.51
Transmitted cases during isolation	1.47	1.12	0.75	0.74
Detected at the first testing	6.72	12.69	6.83	12.98
Detected at the second testing	9.70	0.00	8.49	0.00
Number of missed cases	7.25	12.02	7.95	11.17
Isolation Cost	\$149,000	\$92,368	\$77,892	\$59,664
Testing Cost	\$8,157	\$4,363	\$16,383	\$12,948
Colonization Treatment Cost	\$31,495	\$32,744	\$30,850	\$31,920
Total Cost	\$188,652	\$129,475	\$125,126	\$104,532
Total Annual Loss of QALY	26.36	25.19	23.20	22.52
Number of false positive cases	0.00	0.00	6.90	7.23

The optimal timing of a single culture test is day 3 (Cult3), whereas it is day 2 for a single PCR test (PCR2). Due to the lower sensitivity of culture tests, delaying the culture test by one day enhances its accuracy. However, PCR testing on day 2 still leads to a lower number of MRSA colonizations and reduces the number of missed cases compared to Cult3. Although PCR testing on day 2 incurs higher testing costs due to the expense of PCR tests, it results in a lower total cost by reducing isolation expenses. Although these alternative protocols result in fewer MRSA colonizations than the Cult6 and PCR3 protocols, they still perform worse compared to current practices. This analysis also addresses the choice between single and two-test protocols. Implementing two tests is essential to identify initially colonized cases and break the transmission cycle. However, if only one test is performed, a PCR test is preferred due to its higher sensitivity, which reduces total costs and improves health outcomes.

We also investigate whether replacing the day 0 culture test (Cult0) with a PCR test could improve current MRSA surveillance practices. PCR's higher sensitivity enables identifying higher number of colonized cases due to primary transmissions at the initial testing, reducing both number of colonization during isolation (secondary transmissions) and overall MRSA colonizations. While this substitution reduces the risk of MRSA spread, it increases testing costs due to the higher expense associated with PCR testing. Replacement of Cult0 with PCR leads to an increase in false-positive cases due to the imperfect specificity of the PCR. This increase in false positives results in unnecessary isolation measures and associated costs, ultimately leading to a higher total cost of MRSA management. Our analysis indicates that the initial test on day 0 is critical in breaking the transmission cycle and controlling the spread of MRSA. However, the choice of test modality (Culture vs.

Table 4.5: Performance of current practice with the culture vs PCR testing on day 0 for the base-case scenario.

Performance measures	Cult0+PCR3	PCR0+PCR3
Number of exposed roommates	303.32	302.23
Number of MRSA colonizations	23.44	23.28
Transmissions before isolation	22.69	22.61
Transmissions during isolation	0.75	0.68
True positives at the first testing	6.83	7.84
True positives at the second testing	8.49	7.63
Number of missed cases	7.95	7.66
Number of false positives	6.90	13.71
Testing cost	\$16,383	\$24,333
Isolation cost	\$77,892	\$78,819
MRSA colonization cost	\$30,850	\$30,651
Total cost	\$125,126	\$133,803
Total loss of QALYs	23.20	22.86

PCR) and timing depends on balancing detection accuracy, cost, and the false positives. While a PCR test on day 0 can improve early detection due to higher sensitivity, it may also lead to more false positives, increasing isolation costs. A culture test on day 0, though less sensitive, results in fewer false positives and lower associated costs. The optimal choice thus depends on the primary objective, whether it is minimizing colonization or controlling cost.

4.3.1.4 Effect of Adjusting Initial and Follow-up Test Timing: Culture versus PCR

In this section, we evaluate the impact of using two culture or PCR tests, adjusting the timing of both the initial and follow-up tests to determine the most effective intervals for

MRSA control. Through this analysis, we evaluate the benefits of multiple tests and varied timing to inform protocols that best control MRSA spread while balancing costs. Table 4.6 presents the performance of culture tests with different testing intervals. Compared to the guideline protocol (Cult0+Cult6), adjusting the timing of the initial and follow-up culture tests reduces MRSA colonizations. Instead of removing day 0 testing due to low test sensitivity, our findings indicate that delaying the initial test can improve test accuracy. For example, setting the initial culture test around day 2 yields a detection rate of 62%-65% at the first test, compared to 40.9% with the Cult0+Cult6 protocol. With Cult0+Cult6, fewer cases are detected at the initial test and a longer isolation period, leading to a higher number of transmissions during isolation compared to Cult2+Cult5. Adjusting the timing to Cult2+Cult5 improves the overall detection rate, resulting in fewer missed cases and more effective MRSA control. This protocol also reduces total costs by 12% through savings on isolation expenses. Cult2+Cult4 achieves comparable results in MRSA colonizations while further reducing total costs by 22.4%. Among culture-only protocols, Cult2+Cult4 is the most cost-effective in minimizing MRSA colonizations. With PCR's higher sensitivity, the current practice (Cult0+PCR3) combines early detection with improved accuracy, leading to a shorter isolation duration and offering additional benefits by further reducing both total costs and MRSA colonizations. However, in exchange for improved MRSA detection, Cult0+PCR3 results in more false positives, which should be considered when evaluating overall effectiveness. When both tests are PCR, the optimal timing for minimizing MRSA colonizations is on days 2 and 6 (PCR2+PCR6), with results presented in Table 4.7. Similar to the culture-only protocols, the initial test is performed on day 2. However, since PCR is more effective at detecting cases at the initial test, a

Table 4.6: Performance comparison of the current practices with optimal timing of two culture tests for the base-case scenario.

Performance measures	Cult0+Cult6	Cult0+PCR3	Cult2+Cult5	Cult2+Cult4
Number of exposed roommates	300.24	303.32	296.98	299.60
Number of MRSA cases	23.93	23.44	23.47	23.49
Colonized cases before isolation	22.46	22.69	22.21	22.41
Transmitted cases during isolation	1.47	0.75	1.25	1.08
Detected at the first testing	6.72	6.83	10.50	10.63
Detected at the second testing	9.70	8.49	6.35	5.63
Number of missed cases	7.25	7.95	6.37	7.06
Isolation Cost	\$149,000	\$77,892	\$127,082	\$107,417
Testing Cost	\$8,157	\$16,383	\$8,003	\$8,084
Colonization Treatment Cost	\$31,495	\$30,850	\$30,892	\$30,920
Total Cost	\$188,652	\$125,126	\$165,977	\$146,421
Total Annual Loss of QALY	26.36	23.20	24.18	23.84
Number of false positive cases	0.00	6.90	0.00	0.00

later follow-up test does not lead to increased transmission during isolation, as it would with two culture tests. This approach allows for extended isolation without additional transmission risk, further improving detection accuracy. As a result, PCR2+PCR6 is associated with 33% fewer missed cases compared to the optimal two-culture test protocols. While PCR2+PCR6 is effective, it also incurs higher total costs due to the expense of PCR testing and the extended isolation period. For a cost-effective alternative, protocols such as PCR2+PCR5 or PCR2+PCR4 may be considered, with only a slight increase in MRSA colonizations. These alternatives still achieve a reduction in MRSA cases compared to culture-only protocols, balancing cost savings with effective MRSA control. When we adjust the timing of the initial and follow-up tests, comparing two-test protocols using culture and PCR reveals that using PCR for both tests is the most effective strategy for

Table 4.7: Performance comparison of the current practice with optimal timing of PCR tests for the base-case scenario.

Performance measures	Cult0+PCR3	PCR2+PCR6	PCR2+PCR5	PCR2+PCR4
Number of exposed roommates	303.32	288.91	291.27	293.98
Number of MRSA cases	23.44	22.89	22.93	22.99
Colonized cases before isolation	22.69	21.61	21.79	21.99
Transmitted cases during isolation	0.75	1.28	1.14	1.00
Detected at the first testing	6.83	11.87	12.00	12.14
Detected at the second testing	8.49	6.44	5.87	5.01
Number of missed cases	7.95	4.25	4.85	5.66
Isolation Cost	\$77,892	\$133,047	\$115,113	\$96,869
Testing Cost	\$16,383	\$22,923	\$23,139	\$23,380
Colonization Treatment Cost	\$30,850	\$33,132	\$30,182	\$30,262
Total Cost	\$125,126	\$186,102	\$168,434	\$150,511
Total Annual Loss of QALY	23.20	22.16	21.84	21.69
Number of false positive cases	6.90	12.92	13.13	13.27

minimizing MRSA colonizations cost effectively.

4.3.2 Comparison of Testing Protocols for Different Transmission Probabilities

In Section 4.3.1, we evaluate the effectiveness of various MRSA surveillance practices, addressing several controversial questions and observing that there is no single best protocol. We analyze the performance of considered testing protocols based on the expected number of MRSA colonizations and total cost to gain a comprehensive view of all protocols within this spectrum. Additionally, we conduct an analysis on transmission probability to assess how the optimal number of tests, timing, and test modality change across low, medium, and high-risk settings. Figure 4.2 presents the Pareto frontier analysis across these risk

levels, highlighting the testing protocols that lie on the Pareto frontier.

For the base case transmission probability (Figure 4.2a), the protocols that minimize MRSA colonizations involve two PCR tests with extended isolation periods (PCR2+PCR6, PCR2+PCR5, PCR2+PCR4). These protocols achieve reductions in colonizations by improving test accuracy with extended isolation in a low transmission risk setting. However, they incur significantly higher costs, making them not cost-effective. On the other hand, the protocol with the lowest cost is a single PCR test (PCR0), though this results in a significant increase in MRSA colonizations. The testing protocols closest to the bottom left corner of the Pareto frontier (PCR1+PCR3, PCR0+PCR2, Cult0+PCR2) provide a better balance between MRSA colonization control and cost. Single-test strategies generally do not perform well in achieving this balance.

For low transmission probability, PCR0 performs the worst in terms of MRSA colonizations. However, as transmission probability increases, PCR0 outperforms most other testing protocols. Under medium transmission risk, the best-performing protocols, aside from PCR0, yield similar results, though PCR0 still has higher colonization rates. Protocols involving two PCR tests with extended isolation periods (PCR2+PCR6, PCR2+PCR5, PCR2+PCR4) are eliminated from the Pareto frontier. The longer isolation periods in these protocols lead to increased secondary transmissions, offsetting the advantage of improved testing accuracy. For medium risk, two-test protocols with shorter isolation periods such as PCR0+PCR1 and Cult0+PCR1 provide a cost-effective solution to reduce MRSA colonizations.

In cases of high disease aggressiveness, the optimal strategy in terms of both MRSA

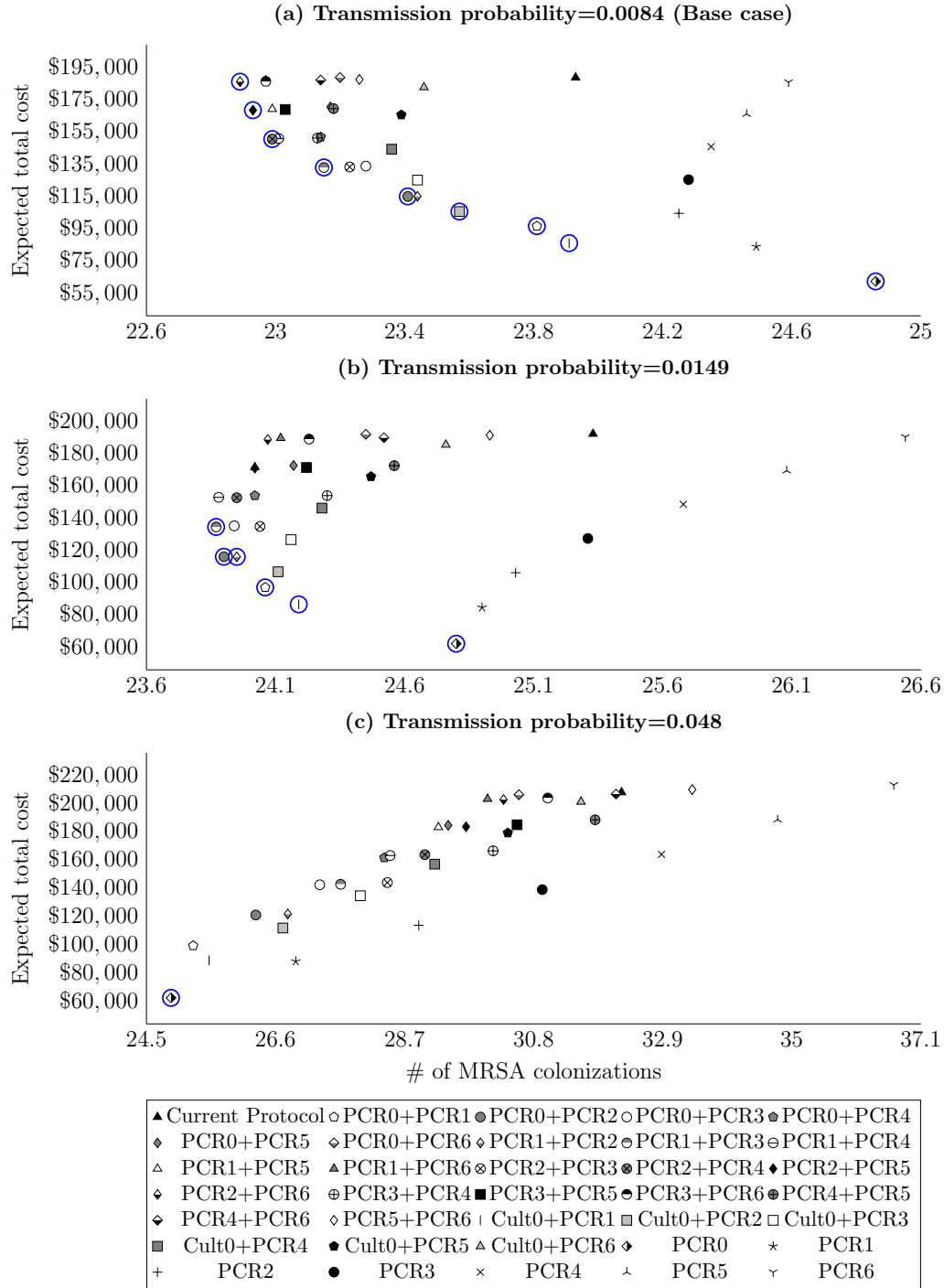


Figure 4.2: Performances of the practical testing protocols in terms of total cost and number of MRSA colonization for different transmission probabilities.

colonizations and cost is PCR0. Testing exposed roommates immediately post-exposure and promptly releasing test negatives given the high transmission risk in cohort and ward rooms. Our analysis highlights the importance of determining an appropriate isolation duration that balances testing accuracy with the risk of secondary transmissions, taking transmission probability into account. When MRSA test sensitivity is lower, undetected carriers pose a significant transmission risk, especially in shared rooms. Conversely, high-sensitivity tests reduce this risk but may lead to unnecessary isolation of patients with non-threatening colonization. Balancing these factors is critical for effective infection control strategies.

4.3.3 Multi-way Sensitivity Analysis

Controlling MRSA colonization is a critical and standard measure of infection control. The analysis in the previous section demonstrates that MRSA colonization is highly sensitive to the disease’s transmission risk and test accuracies. These parameters may change based on the healthcare facility, adherence to infection prevention and control measures and hospital size. A joint analysis of transmission probability and test sensitivities is required in identifying the most effective testing protocol. Based on our analysis of transmission probabilities, we evaluate five testing protocols to identify the optimal strategy for minimizing MRSA colonizations under varying transmission probabilities and culture and PCR sensitivities, as shown in Figure 4.3.

When transmission risk is low, PCR2+PCR6 is the most effective for minimizing MRSA colonizations, unless the culture sensitivity exceeds PCR sensitivity. Cult0+Cult6 out-

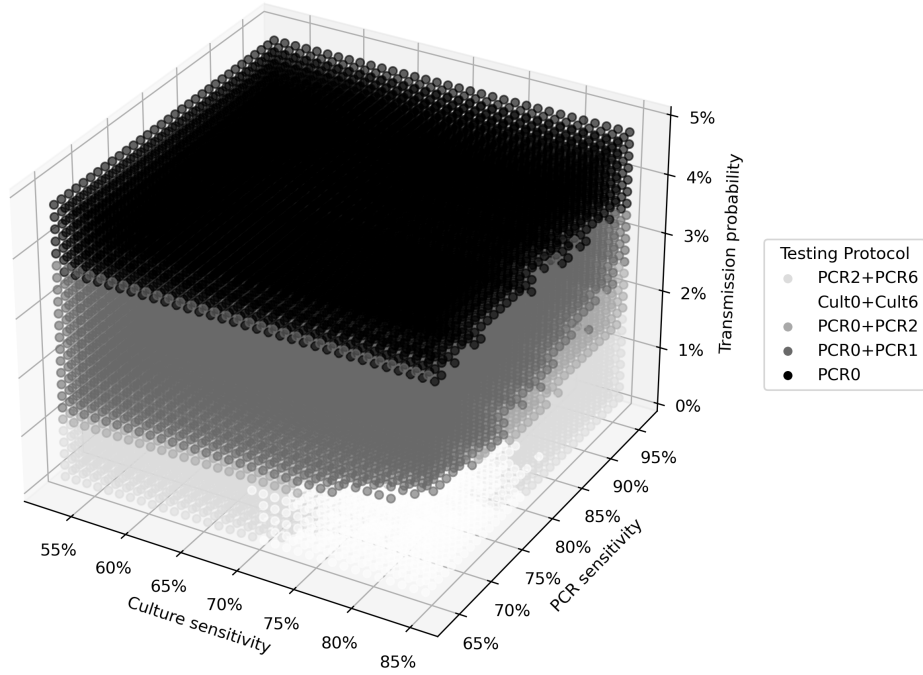


Figure 4.3: Best testing protocol for minimizing MRSA colonizations across transmission probabilities and sensitivity levels.

performs PCR-based protocols only in a rare and unlikely sensitivity scenario but only for transmission probabilities below 1.4%. For realistic sensitivity parameters in low-aggressiveness regions, the best surveillance protocols are PCR-based testing with extended isolation durations. For medium transmission risk, PCR0+PCR2 (up to approximately 2.4% transmission probability) and PCR0+PCR1 are the most effective protocols across the majority of sensitivity parameters. When PCR sensitivity is particularly high, the initial test detects most colonized cases, making a follow-up test on day 2 (PCR0+PCR2) more effective in reducing colonizations. However, as transmission risk increases, the optimal isolation duration shortens, and the effectiveness of PCR0+PCR2 diminishes. Beyond

a 2.6% transmission probability, PCR0+PCR1 outperforms PCR0+PCR2 for all sensitivity scenarios. In high disease aggressiveness scenarios, the optimal strategy shifts to PCR0, where exposed roommates are tested immediately, and test-negative individuals are released without further isolation.

When the objective is to minimize the number of MRSA colonizations, conducting both initial and follow-up tests is the most effective strategy. The analysis also indicates that, for realistic parameter combinations, PCR-based surveillance testing protocols can safely replace current culture-based protocols. In low disease aggressiveness settings, such as those in Canada with high adherence to infection prevention and control measures, PCR2+PCR6 emerges as the most effective protocol. However, the cost-effectiveness of surveillance protocols should also be taken into account when making decisions.

4.4 Conclusion

In this chapter, we introduce a discrete event simulation model integrated with a hidden Markov model to evaluate MRSA surveillance testing protocols for exposed roommates of index MRSA cases. The proposed HMM-based simulation addresses the scalability limitations of the MDP model proposed in Chapter 3 by providing a computationally efficient tool for evaluating MRSA testing protocols in diverse healthcare settings, including larger hospitals. The embedded HMM enables incorporating time-dependent test sensitivities due to increasing bacterial load over time through state definitions. This approach allows for the evaluation of a wide range of testing protocols, including variations in test modalities, timings, and intervals.

We conduct a comprehensive analysis of controversial questions related to MRSA surveillance testing protocols, providing a detailed comparison of various protocols using metrics such as the number of MRSA colonizations, transmissions during isolation, missed cases, and overall MRSA management costs. The testing protocols are evaluated for a large hospital, utilizing disease transmission and progression data from Grand River Hospital, along with cost and disutility parameters derived from clinical literature. We first compare the guidelines (Cult0+Cult6) with the current practice (Cult0+PCR3) at Grand River Hospital (GRH), which yields several practical insights. The results indicate that the Cult0+PCR3 protocol significantly reduces total costs and improves health outcomes compared to the Cult0+Cult6 protocol. The main benefit of Cult0+PCR3 is that it reduces isolation duration by half, resulting in substantial cost savings without compromising test accuracy. These findings suggest that the PCR3 test can safely replace the Cult6 test in MRSA surveillance protocols.

Our results also highlight the benefit of day 0 testing. Although it is associated with lower sensitivity, removing the day 0 test may cause more MRSA colonizations due to increased transmission during isolation. We observe that removing the day 0 test also results in more missed cases and higher total costs. Our findings reinforce the clinical and cost-effectiveness of day 0 testing for the surveillance of exposed roommates, particularly in healthcare facilities with lower adherence to infection prevention and control measures or higher nosocomial MRSA prevalence. Furthermore, replacing the day 0 culture test with a day 0 PCR test can further improve the health outcomes with a slight increase in total cost.

We consider alternative schedules for the culture and PCR tests. Adjusting the timing

of initial and follow-up tests can lead to improvements over current practices. For example, delaying the initial test to day 2 instead of day 0 may reduce secondary transmissions during isolation and lead to lower costs. Our analysis also indicates that replacing culture-based surveillance with PCR-based surveillance is effective in improving health outcomes and achieving cost savings unless the disease transmission probability is low and culture sensitivity exceeds PCR sensitivity. Our multi-way sensitivity analysis identifies the most effective MRSA testing protocol for reducing MRSA colonizations across different parameter settings, including transmission probabilities and culture and PCR test sensitivities.

While focused on MRSA surveillance in this study, the framework is adaptable to other hospital-acquired infections with similar testing and isolation protocols, offering broad applicability in infection control. We use data reflecting a hospital setting classified as a low-risk environment, characterized by low disease aggressiveness and high adherence to infection prevention and control measures. Although our results are based on this specific setting, they can be generalized to other contexts, as many hospitals in Canada have a higher proportion of ward rooms compared to semi-private rooms ([Stall 2012](#)).

In our analysis, we focus on MRSA surveillance protocols involving either a single test or two tests. Future research could evaluate whether adding a third test provides sufficient clinical and cost-effectiveness benefits to justify its use. Additionally, our study does not compare the performance of MRSA testing protocols across hospitals of different sizes, such as small, medium, and large institutions. Analyzing these variations could provide valuable insights into how hospital size influences the effectiveness and efficiency of testing protocols. These aspects are important considerations and are left for future research.

Chapter 5

Conclusions and Future Research Directions

Surveillance testing plays a crucial role in managing and controlling pandemics and outbreaks by enabling early detection, timely isolation, and appropriate contact management, which collectively help limit the spread of disease. This thesis proposes operations research models and methodologies to develop effective testing protocols and optimize the delivery of infectious disease testing. Specifically, we address two key healthcare delivery challenges related to infectious disease testing, providing actionable insights to improve testing effectiveness and support public health decision-making.

Chapter 2 focuses on determining the ideal level of testing capacity to meet varying demand, emphasizing the critical role of COVID-19 testing in mitigating the pandemic's impact and the importance of dynamic capacity management. To address this, we develop

a two-echelon multi-period location and capacity allocation model to determine optimal COVID-19 testing centers and capacities. The model reflects the testing system implemented in Ontario, Canada during the early stages of the pandemic. The objective is to minimize the total number of delayed appointments and collected specimens to be processed subject to budget, capacity, and turnaround time constraints. The model determines several key decisions, including the optimal timing and locations for establishing pop-up testing centers, capacity expansions for existing centers, the assignment of demand regions to testing centers, and the assignment of collected specimens to laboratories. To demonstrate its applicability, the model is implemented in a case study focused on optimizing the locations and capacities of COVID-19 testing centers in the Region of Waterloo, Canada.

We provide managerial insights to the public health decision makers on dynamic capacity management of COVID-19 testing. Key findings are the optimal strategy is to dynamically expand existing specimen collection center capacities and prevent bottlenecks by locating pop-up facilities. Given the increasing frequency and severity of pandemics and epidemics in recent years ([Houlihan and Whitworth 2019](#)), the proposed model offers significant potential for broader application. Beyond its utility for COVID-19, it can be adapted to manage testing capacities for other infectious diseases, providing a flexible framework to address similar challenges in various healthcare contexts. By optimizing the allocation of testing resources and improving accessibility during disease outbreaks, this model contributes not only to immediate response efforts but also to long-term pandemic preparedness, enhancing the resilience of public health systems against future threats.

The main contributions of Chapter 2 are *(i)* the development of a novel mathematical model for efficiently managing testing center location and capacity expansion decisions,

which is applicable not only for COVID-19 but possibly other infectious diseases in the long term, and (ii) a case study covering the Region of Waterloo that provides valuable insights for public-health decision-makers.

Chapter 3 addresses the problem of determining optimal testing protocols for individuals who share a hospital room with patients colonized or infected with MRSA. The focus is specifically on roommates who have been exposed to index cases during their hospital stay. While existing guidelines recommend active MRSA surveillance testing for exposed roommates, they do not specify the optimal timing for specimen collection or the choice of testing modality (culture vs. PCR), leading to variations in testing practices across healthcare facilities and regions. We propose a finite-horizon MDP model to determine the optimal testing schedule, including the timing and frequency of tests, and the resulting isolation duration for exposed roommates. The model incorporates two different objective functions: the first minimizes the loss QALYs from the patients' perspective by balancing factors such as the disutility of isolation, testing, and the risk of missed MRSA cases. The second focuses on minimizing the number of new MRSA colonizations, aligning with clinical priorities for infection control. Since the true health states of the patients are unknown, the problem would require a POMDP. However, to avoid the computational complexity associated with POMDPs, we introduce a novel approach by formulating the problem as an MDP with innovative state definitions. The disease progression and transmission dynamics within isolated rooms are modeled as a HMM, enabling us to incorporate time-varying test sensitivities, as such data for different days is not readily available in the literature. Using the HMM, the MDP model determines the testing and isolation decisions. We optimally solve the model using data from Grand River Hospital and clinical literature.

We conduct several analyses, comparing the performance of the optimal solution with current testing practices and practical testing protocols. These analyses provide valuable insights for clinicians, not only for MRSA testing but also for improving surveillance practices for other hospital-acquired infections. The optimal surveillance protocols are highly dynamic, varying based on factors such as the number of isolated rooms, the number of exposed roommates in those rooms, and the initial test results. While these protocols outperform current practices by reducing total costs and improving health outcomes, their dynamic nature presents practical challenges for implementation. They still provide important guidance for identifying areas where current practices can be improved and determining the extent of those improvements. Using our proposed model, we also identify practical testing protocols performing close to the optimal solutions for both objective functions.

The contributions of Chapter 3 include *(i)* a novel MDP-based stochastic modeling framework for capturing infectious disease transmission and progression, and optimizing intervention plans including testing and contact isolation for a bounded but non-fixed population, *(ii)* a novel core health state definition for capturing the effect of time-varying test sensitivities with a minimal number of model parameters, *(iii)* solving the proposed model exactly by overcoming the curse of dimensionality, and *(iv)* insights for clinicians to improve their practice and identify practical MRSA testing strategies with close-to-optimal performance.

Chapter 4 introduces a hybrid framework that combines a hidden Markov model (HMM) with a discrete-event simulation (DES) to address the scalability challenges of the MDP model for the MRSA surveillance testing problem. The HMM captures the transmission

and progression dynamics of MRSA in isolated hospital rooms, as detailed in Chapter 3, while the DES evaluates testing and isolation decisions and calculates the associated performance metrics. This framework enables the evaluation of various MRSA testing protocols, including different test modalities and intervals, while incorporating varying test sensitivities over time through the HMM. The hybrid HMM-DES framework is utilized to explore and provide insights into controversial policy questions regarding MRSA testing protocols discussed in the literature. Numerical analyses were conducted to evaluate its applicability to large hospitals.

Our findings highlight the marginal benefit of the day 0 culture test and the potential advantages of replacing it with a day 0 PCR test. Additionally, the results emphasize the value of conducting two tests rather than relying on a single test for MRSA surveillance. Exploring alternative schedules for initial and follow-up tests demonstrates further opportunities to enhance testing protocols. Our analysis indicates that culture-based testing can be safely replaced with a PCR-based surveillance protocol, offering improved health outcomes and cost-effectiveness in most scenarios. These insights provide valuable guidance for optimizing MRSA testing practices in hospital settings.

The main contributions of Chapter 4 are *(i)* the development of a computationally efficient HMM-based discrete-event simulation model to evaluate surveillance testing protocols for MRSA and other nosocomial infections in large hospital settings, *(ii)* the evaluation of testing protocols with varying timings and intervals, incorporating time-dependent test sensitivities, *(iii)* insights from extensive numerical analyses addressing key controversial policy questions related to MRSA testing protocols using hospital data, and *(iv)* the identification of the most effective testing protocols under different parameter settings through

detailed analysis.

Although we have already discussed several potential extensions and future research directions specific to each chapter, there are many other promising research opportunities for infectious disease testing in general. Epidemiological models are essential for understanding disease transmission dynamics, predicting future cases, and evaluating the effectiveness of intervention strategies. They have been widely used to guide public health planning and control infectious diseases, particularly during pandemics ([Brauer et al. 2019](#), [Bershteyn et al. 2022](#)). For instance, during the COVID-19 pandemic, many countries relied on these models to forecast case numbers, prepare healthcare systems, and adjust public health measures. Similarly, decision-making models, often developed using operations research (OR) tools, have been employed to optimize resource allocation and strategic planning. However, a significant gap exists in the integration of epidemiological models with decision-making models, limiting their potential to jointly inform dynamic and effective public health decisions. This gap presents an opportunity for the development of these models to improve decision-making processes.

In the proposed location and capacity allocation model in Chapter 2, the testing demand is considered as a given input parameter. In practice, however, the demand is uncertain and it changes depending on various factors such as the disease prevalence and progression, and public health interventions including isolation and vaccination ([Günes et al. 2019](#), [Tuite et al. 2020](#), [Ogden et al. 2020](#)). As future research, a demand estimation model that considers the dynamic aspects of demand and captures the uncertainty associated with it by incorporating the effects of *i*) changing disease prevalence in time, *ii*) COVID-19 variants and vaccination process, and *iii*) social and geographical factors

on the population’s attitude towards testing can be used. A compartmental model, such as an SEIR model, could be designed to incorporate these factors and estimate testing demand more accurately. This would enhance the practicality and applicability of the insights derived from the proposed location model, as policymakers need to account for these dynamic factors when designing effective COVID-19 testing strategies. Additionally, since the locations and capacities of testing centers may influence disease spread and consequently future demand patterns, integrating the optimization model with an SEIR model through a feedback mechanism could provide a more comprehensive framework. This integration would more effectively capture the interaction between testing center location and capacity decisions and the evolving testing demand. It would also enable the evaluation of the combined effects of testing strategies (locations and capacities) and public health interventions. By doing so, policymakers could identify the population dynamics under which these strategies can jointly work to effectively control the pandemic.

In Chapters 3 and 4, we do not consider the individual risk of MRSA acquisition due to underlying medical conditions or length of stay for exposed roommates. Additionally, our models assume that patients are homogeneous in terms of disease propagation and progression. Incorporating these factors would require estimating disease characteristics based on these variables, which is not possible due to limited data availability and the absence of such factors in studies reporting outcomes for exposed roommates. Future research could address this limitation by utilizing detailed clinical data to incorporate patient-specific characteristics and clinical risk factors into the model, capturing variability in infection risk among patients. By integrating these factors, it would be possible to develop personalized testing protocols for infectious diseases, tailoring testing and isolation strategies to

each patient's unique risk profile. Such advancements would enable more accurate analyses and the development of more facility specific testing and isolation protocols.

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APPENDICES

Appendix A

A.1 Testing Demand and Maximum Travel Distance

Table [A.1](#) presents the optimal solutions under additional demand scenarios with min-cost formulation when all demand has to be satisfied on time, i.e., the number of delayed appointments is zero. The first and second columns of the table show the demand week and the percent increase in the demand, respectively. The third and fourth columns specify the average number and utilization of pop-up testing centers opened. The fifth and sixth columns show the average capacity expansion and utilization for existing centers during the planning horizon. The seventh column presents the optimum objective function value (i.e., total cost). Finally, the last column reports the solution time of the model with CPLEX. The first row for each demand set corresponds to the base case results discussed in Section [2.5.1](#).

For the low demand week, compared to the base case, the model does not open additional pop-up testing centers until the demand is increased by 50%, i.e., the increase in testing demand can be served by using the base case pop-up center and expanding the

capacity of the existing assessment centers. For instance, for the 30% demand increase in the low demand week, the model opens the base case pop-up center and expands the capacity of an existing one by 25.3% rather than opening two pop-up centers to avoid a larger fixed cost. For medium and high demand weeks, the average number of opened pop-up testing centers increases with demand. There are several instances (e.g., 30% for high demand week) in which the model prefers using pop-up testing centers over the capacity expansion of the existing ones due to lower unit testing cost. In general, the total cost increases as the overall testing demand increases. The solution times are generally greater for higher demand values of the same demand set and greater for the high demand week from December.

Table A.2 presents the results with different maximum travel distances. All instances in Table A.2 are solved optimally within 8 minutes. The solution times generally increase as the demand level and maximum travel time increase. When the maximum travel distance increases, more people can get access to testing from a particular existing or pop-up testing center. This results in opening fewer pop-up testing centers, as existing capacity can be better utilized to serve remote demand, as well as an increase in the average utilization of the opened pop-ups. On the other hand, when the maximum travel distance decreases, more pop-up testing centers are needed which may lead to lower utilization of some pop-up testing centers. For instance, if the maximum travel distance is decreased to 5 km, pop-ups have a pretty low utilization (e.g., 11% under low demand scenario).

Table A.1: Model outputs under different demand scenarios.

Demand set	Demand level	Avg # of opened pop-ups	Avg utilization of pop-ups (%)	Avg capacity expansion for existing centers (%)	Avg utilization of existing centers (%)	Min total cost(\$)	Solution time (sec)
December (high)	Base case	3	79.3	19.2	71.3	864,513	41.8
	+10%	4	79.6	25	65.7	962,564	41.2
	+20%	4.8	78.7	29	49.7	1,052,885	20
	+30%	5	78.9	18.3	58.8	1,150,867	26
	+40%	6	77.6	18	50.9	1,240,367	22.7
	+50%	7	75.3	17	50.5	1,345,079	237.6
April (medium)	Base case	1.8	76.3	0	58.5	583,731	20
	+10%	2	78.7	10	60.3	648,831	18.7
	+20%	2	80.5	17.5	70.4	698,525	24.4
	+30%	2.3	80.9	19.2	72.9	762,655	34.7
	+40%	2.7	81.1	15.6	69.8	823,957	34.9
	+50%	3.3	81	23.9	65.1	899,370	42.4
August (low)	Base case	1	89.3	0	37.3	320,672	1.2
	+10%	1	90.1	10	39.4	352,877	9.6
	+20%	1	92.5	23.3	43	381,653	13.7
	+30%	1	94.6	25.3	48.5	421,403	19
	+40%	1	95.7	25.7	52	449,362	12.9
	+50%	1.8	78.7	31.1	35.4	497,235	18

Table A.2: Solutions of the model for different maximum travel distances under different demand scenarios

Demand set	Maximum travel distance (km)	Average # of opened pop-ups	Avg utilization of pop-ups (%)	Avg capacity expansion for existing centers (%)	Avg utilization of existing centers (%)	Min total cost(\$)	Solution time (sec)
December (high)	10	6.8	41.9	34	59.9	1,040,807	1.7
	15	4	61.4	12.1	72.9	926,964	21.3
	20 (Base case)	3	80.9	19.2	71.3	879,739	32.2
	25	3	82.7	17.4	67	864,513	41.8
	30	3	82.9	15.5	61.9	864,727	42.2
April (medium)	5	13.7	20.1	0	19.5	864,693	120.4
	10	5.8	31.3	0	46.9	776,223	1.8
	15	3	50.8	0	50.9	649,740	1.7
	20 (Base case)	1.8	76.3	0	58.5	603,062	16.9
	25	1.3	82.2	12.1	68.1	583,731	20
	30	1.3	81.9	12.5	65.1	576,088	16.8
August (low)	5	12	11	10	43.7	576,063	492.3
	10	5	26.3	22.8	38.2	498,107	1
	15	2	47	25	32.9	386,318	1.5
	20 (Base case)	1	89.3	0	37.3	341,029	6.2
	25	1	92.6	0	21.4	320,672	1.2
	30	1	92.8	0	14.6	319,934	1.3
						319,889	1.6