Optimal Interventions to Control Hospital-Associated *Clostridioides difficile* Infection

By

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Abstract

Clostridioides difficile infection (*C. difficile*; CDI) is one of the most common causes of hospital-associated diarrhea in the United States. *C. difficile* spreads via the fecal-oral route through infectious spores shed in the stool of infected or asymptomatically colonized patients. Removing these spores from hard surfaces or hands requires a strong sporicidal cleanser or thorough soap-and-water hand washing, respectively. CDI affects approximately 500,000 patients and results in about 29,000 deaths each year. Hospitals commonly implement infection control policies using interventions such as hand hygiene and environmental cleaning to reduce CDI rates. However, hospitals often have limited resources for infection control and thus have a strong incentive to maximize the impact of every dollar spent. There is very little official guidance for hospital infection control professionals to reference as they create policies.

This dissertation presents studies on alleviating the burden of CDI in US acute care adult hospitals. Each study approaches the problem of CDI from one of two perspectives: by targeting high-risk CDI patients with interventions to prevent further opportunities for CDI exposure, or by selecting the optimal infection control strategy for a specific hospital. The first perspective is explored with an empirical modeling approach to identify novel risk factors related to CDI. This work specifically focuses on the impact of social determinants of health, which are known risk factors for chronic diseases but are understudied for infectious diseases. Using a nationwide Medicare data sample linked to neighborhood-level measures of deprivation, we found that social determinants of health were a significant risk factor for CDI readmissions.

The second perspective is explored in the remaining chapters. We next present our agent-based model (ABM) of hospital-associated CDI (HA-CDI) in a 200-bed community hospital hospital. We use this ABM to investigate the impact of visitor contact precautions, a common infection control intervention. We found that visitor contact precautions were not associated with a significant decrease in HA-CDI in any experiments. Hospitals can likely obtain a larger reduction in HA-CDI by making small improvements to other more effective infection control interventions.

The next section describes the process of validating an ABM with primary hospital data. We first created an ABM of a specific academic hospital in the Midwest. We then validated the modeled rate of HA-CDI against the actual rate of HA-CDI in the target hospital from 2013-2018. We finally validated the interactions between agents and the environment using a measure of colonization pressure known to have significant effect size on individual CDI risk. Our academic hospital model was able to replicate CDI trends in the target hospital, including the large drop from 2015 to 2016 when infection control interventions were improved.

The final portion of this dissertation presents an optimal control modeling framework for characterizing optimal infection control intervention policies over a finite planning period. This section describes model formulation and reformulation as a mixed-integer linear program. We conduct several experiments to characterize the trade-off between implementability and effectiveness for infection control policies.

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Chapter 1

Introduction

Clostridioides difficile infection (*C. difficile*; CDI) is one of the most common healthcare-associated infections in the United States and affects close to half a million patients each year [1]. *C. difficile* is commonly the result of a disturbance to the healthy colon microbiotia. Symptoms can include diarrhea, fever, dehydration, and stomach cramps. Severe CDIs can result in bowel perforation, sepsis, and death, in rare cases. Some CDIs may be asymptomatic. Common risk factors for CDI include advanced age (65 years and up), immunosuppression, recent interaction with a healthcare setting, and antibiotic usage [2, 3]. CDI is normally treated with antibiotics such as oral vancomycin or fidaxomicin, but a fecal microbiota transplant may be an option for immunocompromised patients or those with multiple recurrent CDIs [4, 5]. There is a possibility of CDI recurrence following treatment or a cessation of symptoms, with approximately 20% of initial cases recurring. Throughout the early 2000's CDI burden in the US increased likely because of the growing prevalence of highly infectious strains and availability of sensitive tests [6–8].

C. difficile is spread via the fecal-oral route through infectious spores shed in the stool of individuals infected or colonized with *C. difficile*. In hospitals, these spores can contaminate hard surfaces, like countertops and bedrails, as well as (gloved) hands [9]. These spores are difficult to remove with common hospital cleaners, and require a sporicidal cleanser like bleach [4]. Similarly, common alcohol-based hand sanitizers are not reliably effective at removing *C. difficile* spores from hands and thorough soap-and-water hand washing is strongly recommended [4, 10]. Infectious spores may also be shed by patients who may be asymptomatic, but nonetheless have infectious *C. difficile* in their colon. CDIs that are caused by exposure to *C. difficile* spores within a healthcare facility are referred to as "healthcare-associated" or "hospital-associated." In some portions of this document we will also use the term "hospital-onset" to describe these CDIs.

CDIs can also result from exposure outside of hospitals: these cases are referred to as "community-associated." Since 2011, the prevalence of community-associated CDIs (CA-CDIs) has been gradually increasing [1]. To differentiate between community- and healthcare-associated CDIs, hospitals use a three day threshold: if a patient tests positive for CDI within the first 3 days of their stay, the case is considered community-associated [11]. If the patient tests positive after 3 days, the case is considered a hospital-associated CDI (HA-CDI). Healthcare associated infections (HAIs) like CDI are associated with increased morbidity, mortality, and excess use of healthcare resources. CDI alone is responsible for roughly $6 billion annually in healthcare spending in the US [12]. HAIs have recently been targeted by the Centers for Medicare and Medicaid Services (CMS) through the Hospital-Acquired Condition Reduction Program (HACRP). Starting in fiscal year 2015, CMS adjusts payment rates for Medicare beneficiaries treated at the worst performing hospitals with respect to HACRP indicators, including HA-CDI.

In this dissertation, we explore two perspectives on limiting the burden of CDI in the US: by targeting high-risk CDI patients for interventions to prevent further opportunities for exposure, and by limiting the spread of CDI in hospitals. Targeting at-risk CDI patients can help prevent recurrence and subsequent spread of *C. difficile* upon readmission. Chapter 2 focuses on this perspective by exploring the effect of neighborhood social deprivation on CDI outcomes.

Chapters 3, 4, and 5 focus on the second perspective. To limit spread of CDI, hospitals use a variety of infection control interventions. Hospitals typically develop 'bundles' of intervention programs to deploy simultaneously. Improved hand hygiene, particularly with soap and water, for healthcare workers, patients, and visitors is a common component of many infection control bundles. Other components may include: environmental cleaning of patient rooms (daily and/or after a patient discharge); wearing of gowns and gloves (i.e., 'contact precautions') when interacting with CDI patients (by healthcare workers and/or visitors); and antibiotic stewardship. Infection control bundles are commonly designed, implemented, and financed by hospital infection control programs. These teams can include infection control subject-matter experts, as well as clinicians and administrators. These programs are often underfunded/understaffed and have a strong incentive to maximize the impact of every dollar spent. However, there are limited tools infection control professionals may use to facilitate decision making. Several studies examine the impact of infection control interventions, but these often focus on a single intervention in a vastly different setting [13–15]. While these studies provide immensely valuable information to infection control professionals, the diversity of hospital characteristics hinders direct translation of successful strategies from other healthcare settings.

Simulation provides a way for infection control professionals to test the impact of single or multiple infection control interventions in a specific environment. Chapter 3 analyzes the impact of an individual infection control intervention - visitor contact precautions - using an agent based model (ABM) approach. The model used in Chapter 3 represents a generic, 200-bed community hospital with patients, healthcare workers, and visitors. Chapter 4 presents the creation and validation of an ABM representing a large academic hospital in the Midwestern US. The academic hospital ABM is modeled after the layout of the target hospital and uses parameters estimated from primary hospital data. We discuss the challenges of validating the hospital ABM with limited data and the utility of alternative validation metrics.

Simulation alone however cannot be easily used to make decisions over a long time period and under budget constraints. To this end, in Chapter 5 we present an optimal control model to select infection control interventions under budget constraints over a finite time horizon. We solve the model as a mixed-integer program (MIP) to select intervention bundles of three common infection controls with parameters estimated from one of the two hospital ABMs.

1.1 Infection control interventions

As previously mentioned, hospitals use a variety of infection control interventions to reduce rates of *C. difficile*. In this section, we briefly describe some of the most common infection control interventions.

Environmental cleaning

One of the most common ways hospital eliminate *C. difficile* spores is through disinfection of hard surfaces, such as counter tops and bed rails in patient room and bathrooms. Typically, this is done using bleach or a similarly strong sporicidal product [4].

However, the fumes from these products may be unpleasant to many patients. Additionally, environmental services staff tend to avoid moving items in patient rooms, and excess clutter can lead to insufficiently cleaned rooms. More recently, UV light technology has proven to be an effective element of the environmental cleaning practice [16]. For much of this dissertation, we differentiate between disinfection attempted every day ('daily cleaning') and after a patient has been discharged and the patient room is being turned-over ('terminal cleaning').

Hand hygiene

Improving hand hygiene is one of the most common ways hospitals work towards reducing CDI rates. Improvement programs can target clinicians, patients, or visitors. Hand hygiene improvement programs can be implemented in a variety of ways, including posters, meetings, observation, and physical layout changes [17, 18]. Alcohol-based hand sanitizer rubs are popular within hospitals, but these are known to relatively ineffective at eliminating *C. difficile*. Therefore, hospitals typically promote thorough soap-and-water hand washing for about 30 seconds [10]. Hand hygiene best practices are likely well understood by all clinicians in a hospital, but they may be easy to skip if the clinician believes a patient visit will be very brief.

Contact precautions

Another way to prevent the transfer of *C. difficile* to an individual's hands is to require the wearing of hospital gowns and gloves when interacting with a known CDI-positive patient. We refer to this practice as wearing 'contact precautions.' Hospitals can require clinicians and/or visitors to wear contact precautions before entering the room of a CDI patient. Putting on, or 'donning' contact precautions is not trivial, as many hospital gowns are secured with tie closures in the back and can be easily forgotten if the wearer is not careful. Gowns and gloves must be carefully removed and disposed immediately after exiting the patient's room. There is a growing body of literature demonstrating that contact precautions can have a very small impact on rates of HA-CDI [19, 20].

Screening at admission

As a result of the growing rate of CDI in the community, it may often be beneficial to identify patients colonized/infected with *C. difficile* when they arrive at the hospital. This early knowledge prompts clinicians and environmental services staff to adhere strongly to infection control best practices and reduce the downstream spread of *C. difficile*. CDI tests are performed by hospital labs using a patient stool sample, and typically have a high sensitivity and specificity [21]. Screening has been repeatedly identified as a (cost-)effective strategy for reducing HA-CDI rates [22–24].

Chapter 2

Neighborhood disadvantage and 30-day readmission risk following *Clostridioides difficile* infection hospitalization [1]

2.1 Introduction

Clostridioides difficile is a major cause of healthcare-associated diarrhea in the United States, responsible for nearly 500,000 cases of C. difficile infection (CDI), 30,000 deaths and over $5 billion each year [1]. One reason that curtailment of CDI remains a major challenge is the high rate of CDI recurrence, which occurs in up to 30% of patients [26]. Patients with recurrent CDI may need to be subsequently readmitted to a healthcare facility, which presents an opportunity for continued transmission of CDI in the inpatient setting and new infections in susceptible hosts. Data on readmissions following an inpatient stay with CDI, while limited, show that approximately 23% of patients had at least one readmission, with approximately 32% of readmissions carrying a principal diagnosis of CDI [27]. Patients with a CDI discharge have been found to have a 16 percentage point higher rate of 30-day readmission than patients without a CDI discharge [28].

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[1] **All the work included in this chapter has been previously published in the journal BMC Infectious Diseases under a CC-BY License permitting reproduction of the content in this dissertation [25].**

Commonly cited risk factors of recurrent CDI include older age and continued use of antibiotics [29]. Few studies that focus on risk factors of CDI recurrence consider the impact of social determinants of health. Social determinants are increasingly recognized as major contributors to readmissions for chronic conditions like congestive heart failure and myocardial infarction. However, little data exist on the relationship between social determinants of health and outcomes of acute infectious conditions (other than pneumonia-a condition that Centers for Medicare & Medicaid Services (CMS) penalizes for readmission) in developed countries such as the US. Because CDI diagnosis is associated with high rates of recurrence, it is plausible that the rate of readmission following a CDI-related stay would be similar to that for chronic conditions and that socioeconomic disadvantage would be an important contributor to the risk of recurrence and thereby readmission.

Socioeconomic disadvantage likely adversely impacts a CDI patient's post discharge course. Challenges may include financial constraints to completing the full antibiotic course, especially as the most common treatments for CDI, oral vancomycin and fidaxomicin, can be prohibitively expensive for uninsured patients [30, 31]. Other challenges may include inability to manage environmental cleaning to reduce re-infection and spore shedding, and lack of resources such as transportation and social support to facilitate follow-up care [30, 32]. Household crowding, a common indicator of socioeconomic disadvantage, has also been linked to poorer outcomes for infectious disease patients [33]. As CDI is a disease caused by perturbation of the gut microbiome, factors that impede restoration of the gut microbiome may also affect CDI outcomes. Patients living in socioeconomically disadvantaged neighborhoods have higher rates of comorbid conditions, increasing their contact with the healthcare system and risk of CDI and/or antibiotic exposure. A growing body of literature suggests that diet is a major driver of gut microbiome composition and health [34, 35]. Patients living in socioeconomically disadvantaged neighborhoods are more likely to live in “food deserts,” where access to healthy, high fiber foods may be limited [36]. Consumption of low-fiber, highly processed foods has been found to be strongly linked to socioeconomic disadvantage [37]. As these potential mechanisms impact specific characteristics of CDI, it is likely that disadvantage would adversely affect a CDI patient’s outcomes. Therefore, we hypothesized that socioeconomic disadvantage as measured by residence in a disadvantaged neighborhood would be associated with a higher risk of readmission for CDI patients.

2.2 Methods

We conducted a retrospective observational study to evaluate the association between neighborhood socioeconomic disadvantage and risk of readmission for patients discharged after a CDI-related stay.

Data source and cohort creation:

We measured the relative socioeconomic disadvantage at the Census Block Group, or “neighborhood,” level using the Area Deprivation Index (ADI). ADI was developed three decades ago and subsequently has been validated at the more granular Census Block Group level [38]. ADI is a composite index that draws from several weighted indicators of neighborhood socioeconomic disadvantage, including constructs of income, employment, education and housing quality [39]. ADI is validated at the neighborhood level and has been used in several other studies [40–42].

The cohort included all patients within a 20% Medicare claims national random sample who had a CDI-related index inpatient stay (ICD-9-CM=008.45) between January 1-November 30, 2014. Beneficiaries with valid ZIP+4 codes (95%) were geolinked to corresponding neighborhood national ADI ranking, obtained from the UW Neighborhood Atlas [43]. As consistent with CMS readmission metric policy, patients not meeting the following criteria were excluded: stays from non-federal short-term acute hospitals, those without continuous Medicare part A and B enrollment, those who died during their index stay, or were discharged against medical advice. Other exclusions included: patients without valid geolinked ADI national percentile scores, age less than 18 years, those with railroad retirement benefits, or those enrolled in Medicare HMO. As multiple hospital stays by a single patient could invalidate the assumption of independence for all records in our dataset, we retained only the first stay for patients that had multiple hospital stays during the study period. Figure 1 describes the creation of our study cohort.

Variables

The primary outcome measure was odds for 30-day all-cause readmission as defined previously and which is used by CMS to inform readmission-based policies [44, 45]. We considered all-cause readmissions because of the wide range of reasons patients with recurrent CDI can be readmitted. Our key explanatory variable was neighborhood-level socioeconomic disadvantage as measured by ADI.

Covariates selected for model adjustment were chosen based on previous literature and conceptual models of readmission [38,46]. Illness burden was captured via Elixhauser comorbidity categories in the 12 months prior to each index hospitalization [47]. Patients were considered dual Medicare-Medicaid enrolled if they were enrolled in Medicaid in any of the 12 months preceding index hospitalization. Patients were considered disabled if their reason for Medicare entitlements was disability related. Additional patient-level adjustments were made for age, race/ethnicity, and rurality via Rural-Urban Commuting Area (RUCA) codes. Age was split at 65 as advanced age is widely cited as a risk factor for incident and recurrent CDI [26, 48]. Factors associated with hospital stay included length of stay (LoS) and discharge to a skilled nursing facility (SNF) after index hospitalization. Factors related to hospital characteristics included hospital Medicare beneficiary discharge volume (grouped into tertiles), medical school affiliation (major, minor, or none), and hospital type (non-profit, for-profit, government).

Statistical analyses

We graphically depicted the 30-day readmission rate as a function of patient ADI national ranking to evaluate the unadjusted relationship between the outcome and our key explanatory variable. The cohort was split into two groupings on the basis of neighborhood disadvantage; patients living in the 85% least disadvantaged neighborhoods and those living in the 15% most disadvantaged neighborhoods. The threshold of 85 was selected based on existing literature that showed patients living in the most disadvantaged 15% of neighborhoods had significantly increased risk of readmission for common chronic conditions [38]. To test the stability of results, we conducted a sensitivity analysis on the choice of threshold.

For both ADI groupings of neighborhood disadvantage, we examined descriptive means and proportions to assess how the two groups differ on key baseline patient and hospital characteristics. We then used multivariable logistic regression techniques to further examine the relationship between ADI grouping and 30-day readmission rate.

All odds ratios and predicted probabilities were calculated twice; once using a generalized estimating equations approach with clustered standard errors at the hospital-level and once using a general linear model with robust standard errors [49, 50]. Since no difference was found between the results of the two models, we present the general linear model results. We calculated predicted probabilities using marginal standardization methods [51].

Finally, we performed a series of subgroup analyses on a-priori subgroups that may have a differential odds of readmission for those living in the most disadvantaged neighborhoods using established methods to test for interaction effects [52]. These groups were patient dual Medicare-Medicaid enrollment status, SNF discharge status and race. Race and dual Medicare-Medicaid enrollment were analyzed because of their association with increased likelihood of residence in a disadvantage neighborhood as previously reported [38]. Discharge to SNF status was analyzed to assess the impact of the patient's post-discharge environment, as patients living in disadvantaged neighborhoods that are discharged to SNFs could be insulated from any adverse effects of their residential environment. Analyses were conducted using SAS version 9.4 (SAS Institute) and StataSE 15 (StataCorp).

IRB approval

This study has been approved by the University of Wisconsin Health Sciences Institutional Review Board.

2.3 Results

Cohort creation and characteristics

Our final cohort included 19,490 unique Medicare-insured patients with a CDI-related index stay discharged from 2,855 unique health care facilities (see Figure 1 for detailed sample derivation). Less than 0.04% of patients in the cohort were missing age and LoS data. Patients with missing age or LoS data were grouped into the 65 years and above age category or the fewer than three days LoS category, respectively. From our cohort, 22% were readmitted within 30 days (unadjusted). Patients living in the most disadvantaged 15% of neighborhoods were readmitted at an observed rate of 26%, while patients living in the least disadvantaged 85% were readmitted at an observed rate of 21%. Figure 2 depicts the observed readmission rate over the range of ADI national percentiles.

Descriptively, the most disadvantaged 15% of neighborhoods had higher rates of dual Medicare-Medicaid enrollment, of patients younger than 65 years, and of patients of black race relative to the least disadvantaged 85% of neighborhoods (Table 1). This patient population also had higher rates of nearly all comorbidities, including chronic conditions such as diabetes and hypertension.

Patients living in the 15% most disadvantaged neighborhoods also had higher rates of discharge from a hospital with relatively low discharge volumes. Patients living in the 85% least disadvantaged neighborhoods had a higher rate of discharge to a SNF relative to patients living in the most disadvantaged 15% of neighborhoods. These patients also had a higher rate of residence in an urban neighborhood.

Table 1: Cohort description

Variable	ADI National percentile <85 (n = 17,094)	ADI National percentile $\geq$ 85 (n= 2,396)
Patients		
Age		
Mean Age at Discharge (SD), y	75.64 (12.83)	71.79 (13.90)
18-65 y	16%	26%
65+ y	84%	74%
Sex		
Male	39%	39%
Female	61%	61%
Race		
White	83%	58%
Black	10%	28%
Other/Unknown	8%	14%
Medicaid Enrollment		
Not Medicaid Enrolled	74%	51%
Medicaid Enrolled	26%	49%
Disability		
Not disabled	72%	57%

Table 1 continued from previous page

Variable	ADI National percentile <85 ($n = 17{,}094$)	ADI National percentile ≥ 85 ($n = 2{,}396$)
Disabled	28%	43%
Patient RUCA		
Urban core	73%	65%
Suburban	9%	6%
Large rural	10%	14%
Small rural	8%	15%
Elixhauser Comorbidities		
Hypertension	79%	84%
Fluid and electrolyte disorders	59%	65%
Deficiency anemia	52%	58%
Diabetes (without chronic complications)	37%	46%
Renal failure	36%	42%
Chronic pulmonary disease	34%	42%
Congestive heart failure	30%	36%
Depression	26%	29%
Other neurological conditions	25%	28%
Hypothyroidism	25%	23%
Peripheral vascular disease	22%	26%
Weight loss	20%	25%

Table 1 continued from previous page

Variable	ADI National percentile <85 (n = 17,094)	ADI National percentile ≥ 85 (n= 2,396)
Obesity	17%	21%
Diabetes (with chronic complications)	17%	24%
Valvular disease	15%	14%
Metastatic cancer	5%	4%
Alcohol abuse	4%	6%
Drug abuse	4%	6%
Chronic blood loss anemia	4%	5%
Lymphoma	3%	3%
Acquired immune deficiency syndrome	1%	2%
Pulmonary circulation disease	10%	11%
Rheumatoid arthritis/collagen vascular disease	8%	9%
Paralysis	8%	10%
Liver disease	7%	9%
Solid tumor without metastasis	14%	11%
Psychoses	11%	14%
Coagulopathy	14%	15%
Index Stay		
Length of Stay		

Table 1 continued from previous page

Variable	ADI National percentile <85 (n = 17,094)	ADI National percentile ≥ 85 (n= 2,396)
Mean Hospital length of stay (SD), days	9.68 (9.60)	10.38 (11.80)
≤ 2 days	8%	7%
3-4 days	21%	18%
5-6 days	18%	18%
7+ days	53%	56%
SNF Discharge		
Discharged to SNF	37%	33%
Not discharged to SNF	63%	67%
Index Hospital		
Medical School Affiliation		
Hospital affiliated with medical school	50%	56%
Minor medical school affiliated	27%	30%
Major medical school affiliated	23%	26%
Hospital Type		
Non-profit hospital	75%	68%
For profit hospital	13%	17%
Government hospital	12%	15%
Discharge		

Table 1 continued from previous page

Variable	ADI National percentile <85 (n = 17,094)	ADI National percentile ≥ 85 (n= 2,396)
Hospital discharge volume in 2014 (SD)	6463.18 (4791.26)	6554.34 (4968.94)
Hospital discharge volume: lowest tertile	8%	10%
Hospital discharge volume: middle tertile	23%	21%
Hospital discharge volume: highest tertile	69%	69%
Outcome		
Rate of 30-day readmission	21%	26%
Rate of 30-day death	13%	13%

Patient neighborhood disadvantage and 30-day readmission risk

Patients living in the most disadvantaged neighborhoods had a significantly increased odds of 30-day readmission compared to patients living in less disadvantaged neighborhoods (unadjusted OR = 1.32, 95% CI: [1.20, 1.45]) (Table 2). When adjusted for all covariates, living in the most disadvantaged neighborhoods was associated with a 16% increased odds of readmission relative to those from the least disadvantaged neighborhoods (OR = 1.16, 95% CI: [1.04, 1.28]). This translates into a 2.5% increase in the predicted probability of a readmission (from 21.6% to 24.1%). The effect is similar in magnitude to that of diabetes with chronic complications (OR = 1.12, 95% CI [1.01, 1.25]) and renal failure (OR = 1.19, 95% CI: [1.10, 1.29]) (see 22). Results were robust to the choice of threshold: patients living in the least advantaged neighborhoods were consistently estimated to be at greater risk (23).

Table 2: Odds of 30-day readmission for CDI patients by ADI score national percentile

Variable	Odds ratio (95% CI)	Predicted Probability (%) (95% CI)
Unadjusted		
ADI <85 percentile	Reference	21.3 (20.7, 21.9)
ADI $\geq$ 85 percentile	1.32 (1.20, 1.45)	26.3 (24.5, 28.1)
Adjusted		
ADI <85 percentile	Reference	21.6 (21.0, 22.2)
ADI $\geq$ 85 percentile	1.16 (1.04, 1.28)	24.1 (22.4, 25.8)

Results of the subgroup analyses showed no evidence for a significantly modified effect by the beneficiary's SNF discharge status, dual Medicare-Medicaid enrollment status, or race (24).

2.4 Discussion

We found that living in a disadvantaged neighborhood was associated with increased odds of readmission for patients with a CDI-related index hospital stay and this remained true after adjustment for patient-, stay-, and hospital-level variables. To our knowledge, this is the first study to explore the relationship between social determinants of health as measured by neighborhood disadvantage and risk of readmission for patients with an index CDI-related hospitalization.

Our analyses found that both neighborhood disadvantage and dual Medicare-Medicaid enrollment (a proxy for low-income individuals and common indicator of social risk) were significant predictors of readmission. This suggests ADI captures a dimension of socioeconomic disadvantage that dual Medicare-Medicaid enrollment status and potentially other individual social risk factors cannot. This ability may be driven in part by the impact of neighborhood disadvantage on a patient's ability to follow post-discharge care and the success probability of that care.

Our findings have implications for clinicians, infection preventionists, and healthcare institutions. For clinicians, the approaches to mitigating risk to CDI patients living in disadvantaged neighborhoods may need to vary from those applied to similar patients with chronic conditions. For example, follow-ups with primary care, potentially using telemedicine resources, might need to be conducted sooner compared to other conditions. Such approaches may need to be conducted in addition to those targeting the impact of neighborhood disadvantage across all conditions. From the infection prevention perspective, placing CDI patients in contact precautions and promoting enhanced hand hygiene practices by healthcare workers is variably effective in reducing transmission, in part because of challenges in high fidelity implementation and breaches in prevention practices. Therefore, preventing readmissions as an upstream intervention is key. Additionally, unlike many chronic conditions, readmission of patients with a contagious disease such as CDI has implications not just for individual patients but for all hospitalized patients including others at risk for readmission. Asymptomatic colonized patients have been shown to contribute significantly to the overall burden of CDI in healthcare institutions, emphasizing the need to prevent unnecessary readmissions [53]. Preventing readmissions for all patients is also important as a marker for quality and because of the financial implications related to increased rates of readmission. The rates of readmission in this study of Medicare enrollees with an index stay of CDI exceeds the rate of readmission of 17% found in the general Medicare population [54]. We also found that the length of stay in our study was approximately three days longer than that found in the general Medicare population [55]. As the US healthcare system moves to value-based purchasing with a reduced likelihood that payers will cover costs of readmissions, and the financial penalties to healthcare institutions for CDI, it is important to understand factors that increase readmission risk. The ability to identify specific patients with increased risk for readmission could be a valuable tool to allocate resources such as transitional care programs, intensive case management, and social work to those patients.

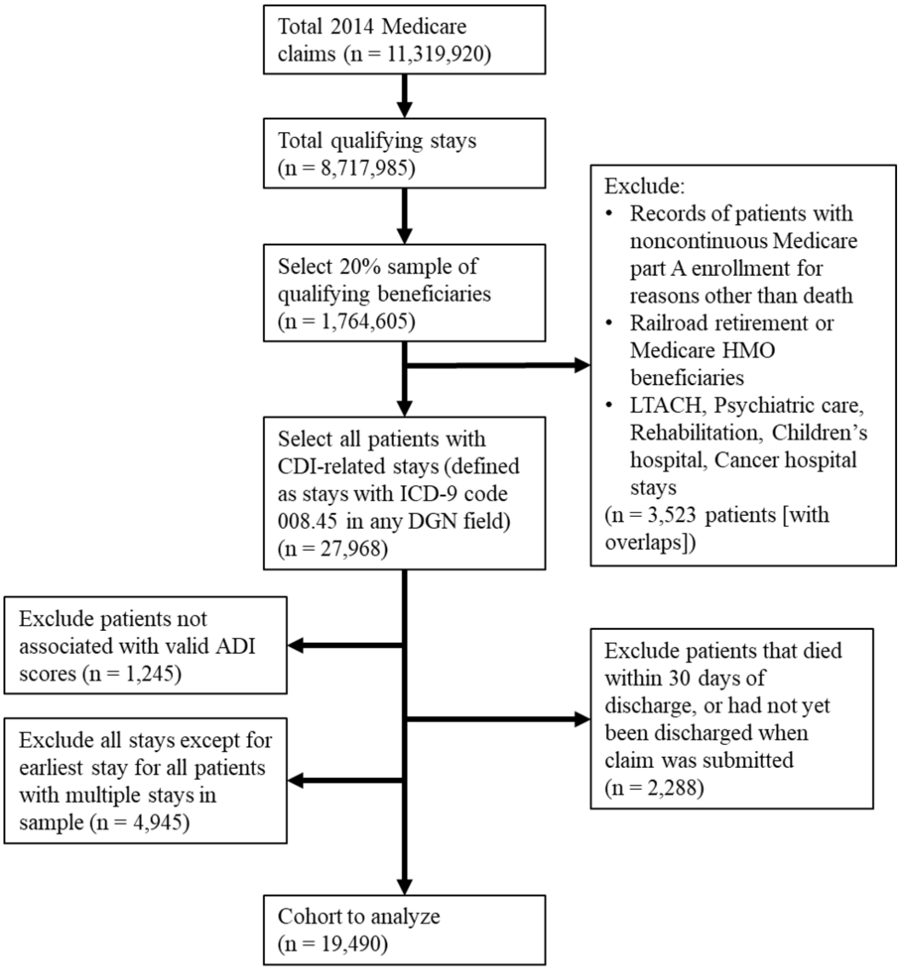
Our findings are supported by other studies of readmissions in CDI that report rates of 25-30% readmission and prolonged duration of hospitalization. In a retrospective cohort study of 385,682 initial CDI hospitalizations identified between years 2009 and 2013 in the 4 states included in the State Inpatient Database (AHRQ), 25.7% of patients required readmission; among these, 36.8% had recurrent CDI as the principal diagnosis at the time of readmission [56]. A study of data from the Healthcare Cost and Utilization Project (HCUP) saw that patients with a primary or secondary diagnosis of CDI had a 30-day readmission rate of 29.1% [57].

We were not able to determine the extent to which recurrent CDI was the cause of the readmissions. Given the high recurrence rate associated with CDI, it is plausible that recurrent CDI contributed to the readmissions for at least some patients. Prediction models for recurrent CDI have been developed but have had variable performance to consistently predict patients at risk for CDI [58, 59]. These models have largely focused on patient level factors such as severity of CDI or comorbidities that may increase readmission risk. Our study examining the relationship between neighborhood disadvantage and readmission extends the knowledge base in this area and offers an opportunity to develop and test interventions targeting social determinants of health in the Medicare-enrolled CDI population. Most other studies of interventions designed to prevent readmissions have focused on acute myocardial infarction, pneumonia, and congestive heart failure [38, 60]. Infectious conditions (other than pneumonia) have not been included in these interventions. In the case of CDI, where symptoms may be prolonged or recurrent and the implications of readmissions extend beyond the individual patient, additional interventions like those used for chronic conditions may be useful.

To develop such interventions, further research is required to understand the precise mechanisms by which neighborhood disadvantage affects readmission risk in CDI patients. These mechanisms require additional research specifically designed to explore them since those proposed in this study remain conceptual. The actual mechanisms of increased risk, which could resemble those proposed earlier, likely differ somewhat from those affecting chronic conditions because of the infectiousness and recurrence patterns of CDI. Future research efforts should subsequently focus on developing and testing interventions to prevent readmissions of CDI patients living in disadvantaged neighborhoods such as specialized allocation of resources to improve the transition of care after hospitalization and access to follow-up in the outpatient setting. Studies should then examine the impact of these new interventions on CDI rates in healthcare institutions and how these interventions affect other healthcare-associated infections. This is especially important regarding other infections associated with high rates of recurrence, or with extensive or crucial post-discharge care procedures.

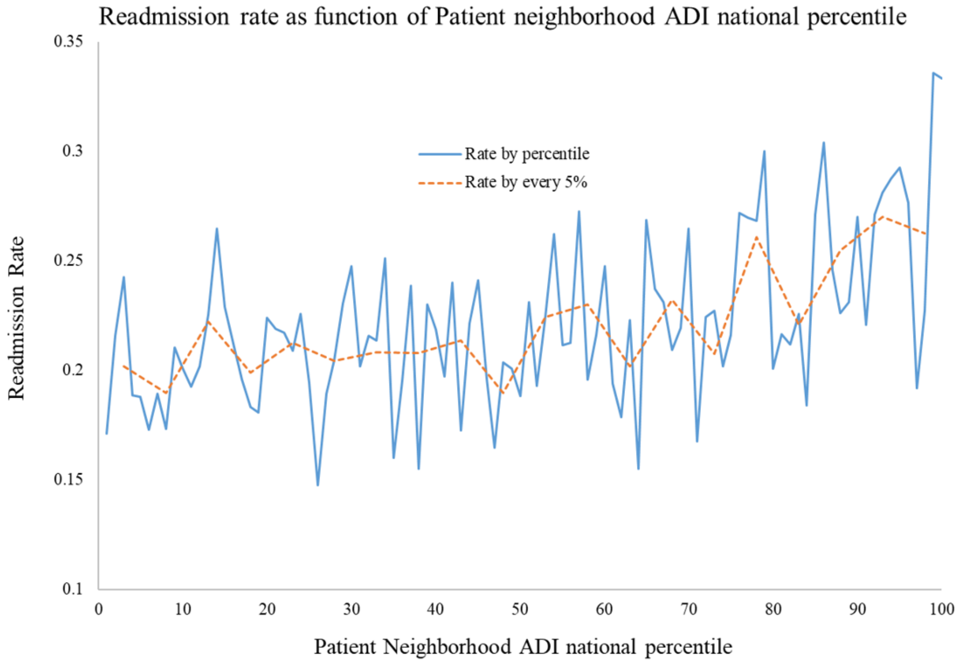
Our study has limitations. We did not have patient data on treatment factors, lab tests and vital signs to include in the analyses, any of which could explain the relationship between ADI and readmission risk. Given the lack of data on direct quality measures that may impact the risk of readmission, we could not analyze the quality of care as a marker for readmission in patients with a CDI-related index stay. Our choice of the 85th ADI national percentile as the threshold to split our cohort may have also impacted the findings from our study. However, other studies have used various methods for grouping their cohorts by ADI national percentile, often focusing on the 85th ADI national percentile and up [38, 61]. Another limitation of this study is the reliance on ICD-9 codes to indicate CDI, rather than lab data. However, ICD-9 codes have been shown to have reasonable sensitivity and specificity for indicating a diagnosis of CDI [62]. This dataset also does not allow us to identify planned readmissions. Planned readmissions (for non-CDI related purposes) could bias the effect size of any of our independent variables if planned readmissions are not uniformly distributed across our covariates; however planned readmissions in patients with CDI are not common. Focusing this study on Medicare patients may also be a limitation. However, as advanced age is considered a risk factor for CDI susceptibility, it is likely that the Medicare population well reflects the overall CDI susceptible population. Finally, similar to most other studies focusing on the Medicare population, we considered all cause readmissions and did not determine relatedness to CDI [38,42]. A justification for this approach is that CDI may influence readmission even if it is not considered as the primary cause of it, as might occur in patients with partially resolved CDI at the time of discharge. Anorexia, dehydration, and weakness related to CDI may exacerbate other chronic comorbidities and lead to readmission. These limitations notwithstanding, this study is among the first to show that neighborhood disadvantage is associated with an increased risk of readmission in inpatients with an acute infectious transmissible condition such as CDI.

Residence in a disadvantaged neighborhood significantly increases the risk of readmission in patients with an index CDI-related hospital stay. The effect size of neighborhood disadvantage was similar to those of chronic conditions and individual dual Medicare-Medicaid enrollment. Interventions that target the aggravating mechanisms of neighborhood disadvantage on CDI outcomes should be considered. Programs that are designed to reduce unwanted readmissions for chronic conditions, several of which are already in place in many healthcare institutions, may also benefit patients with CDI and should be evaluated for their impact on this population.



ADI = Area Deprivation Index
LTACH = Long term acute care hospital
HMO = Health Maintenance Organization
DGN = Diagnosis code

Figure 1: Creation of cohort



ADI = Area Deprivation Index

Figure 2: Readmission as function of ADI percentile

Chapter 3

Estimation of hospital-onset *Clostridioides difficile* infection rates in acute care hospitals associated with and without visitor contact precautions [1]

3.1 Introduction

Clostridioides difficile infection (*C. difficile*; CDI) is a major healthcare-associated infection and its containment is considered a public health priority [64]. In healthcare settings, *C. difficile* transmission is believed to occur primarily through the physical interactions between patients, healthcare workers, visitors, and the environment. Recent guidelines from leading infectious diseases societies recommend several infection control interventions to curtail *C. difficile* transmission [4, 65]. Thus, many institutions have developed CDI prevention bundles, which incorporate multiple intervention strategies simultaneously. Implementing complex bundles with high fidelity requires extensive resources [20]. However, infection control programs are drastically underfunded at hospitals, with only half budgeting money specifically for an infection control department [66].

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[1] **All the work included in this chapter has been previously published in the journal JAMA Network Open under a CC-BY License permitting reproduction of the content in this dissertation [63].**

In the setting of known financial constraints, it is crucial to identify and prioritize the most promising interventions to reduce hospital-onset CDI (HO-CDI).

CDI infection prevention bundles typically include a visitor contact precautions (VCPs) component, which require visitors to don gowns and gloves upon entering a CDI patient's room. In a recent survey of 245 North American hospitals, 71% offered visitors education materials about contact precautions for *C. difficile* and 82% had specific contact precaution policies for visitors of patients with CDI [65]. The 2014 infectious diseases guidelines consider the use of contact precautions for visitors upon entry into the room of a patient with CDI as an "unresolved issue" without substantial supporting evidence; infection control guidelines recommend the use of VCPs for CDI patients, but also note a lack of strong supporting evidence [65, 67]. The 2017 infectious diseases guidelines specifically recommend contact precautions for healthcare workers [4].

Placing patients with CDI in contact precautions for care by healthcare workers is essential to reduce patient to patient and patient to healthcare worker transmission. However, visitors, unlike healthcare workers, do not interact with multiple patients and do not usually participate in the physical care of the patient. Thus, the benefit of VCPs is unclear. Moreover, there may be a detrimental effect of VCPs on patients if their visitors are required to don gowns and gloves before interacting with the patient. Unlike many other infection control interventions, in addition to the cost and resource implications, there is a strong quality-of-life effect of contact precautions as well. Some studies have reported increased delirium and depression in patients placed in contact precautions; other studies have not found such a link [68–71]. Though most existing studies focus on healthcare worker contact precautions, it is possible that the adverse effects of contact precautions are aggravated by VCPs, as isolation between patients and their visiting family and friends could be particularly distressing [72]. Receiving visitors has been linked to greater satisfaction among patients, but patients under contact precautions may receive a smaller number of visitors [73, 74]. Any potential benefits in VCP must be considered in the context of these detriments in patient outcomes. The risks and costs of VCPs in typical conditions may outweigh the benefits for two other healthcare-associated infections, Methicillin-resistant staphylococcus aureus (MRSA) and Vancomycin-resistant Enterococcus (VRE): recent guidelines recommend against VCPs for endemic MRSA and VRE, since these infections are prevalent in the community [65].

Data on the contribution of VCPs to CDI transmission are essential to guide decision-making regarding this intervention. To our knowledge, no study has estimated the contribution of VCPs to hospital-onset CDI. The purpose of this paper is to use simulation modeling to estimate the association between VCPs and HO-CDI. Estimating this association is challenging, because the magnitude may differ according to hospital and community characteristics. For example, there is likely a differential impact of VCPs on HO-CDI rate in a hospital where most patients are susceptible to CDI versus a hospital where a very small proportion of the patients are susceptible. Simulation modeling is inherently able to test large numbers of configurations and as such is an essential alternative to conventional epidemiologic studies in this context.

3.2 Methods

Overview of the Agent-Based Simulation Model

We used our group's previously developed agent-based simulation model of *C. difficile* transmission in an acute care, tertiary adult hospital [20]. This model replicates CDI-related events in a 200-bed dynamic hospital environment representing an average size US adult hospital and includes four types of agents: patients, visitors, nurses, and physicians (Figure 3) [20]. The model represents the CDI-related status of the patients using one of nine possible disease states. The model updates the clinical state of each patient in the hospital every six hours using a discrete-time Markov chain structure (eTable A1, eFigure A1, in online supplement). Patients in the colonized, infected, recolonized, or recurrent infection states can transmit *C. difficile* to other agents and the environment through interactions with them. Visitors, nurses, and physicians who are contaminated with *C. difficile* from patients or the environment can in turn transmit *C. difficile* to other susceptible patients and the environment. Similarly, any agent interacting with a contaminated environment can become exposed to *C. difficile.* The probability of transmission for each interaction depends on the agent types involved and the duration of the interaction. ETable A2 presents the key parameters related to *C. difficile* transmission and other model inputs.

The initial model was developed using NetLogo Software (Version 5.3.1) and subsequently translated into the Java programming language for faster speeds and flexibility as described in online supplement Section B [20]. All experiments were conducted using the Java version of the model. The original NetLogo model was validated through face validation, parameter sensitivity analyses, and cross-validation, which involved comparing model output to those from CDI infection control studies in the literature. Both versions use common random numbers generated by the Colt Project's Mersenne Twister algorithm to reduce variation and to directly compare runs under different intervention scenarios [20]. For a detailed description of the model, see our prior publications [20,24].

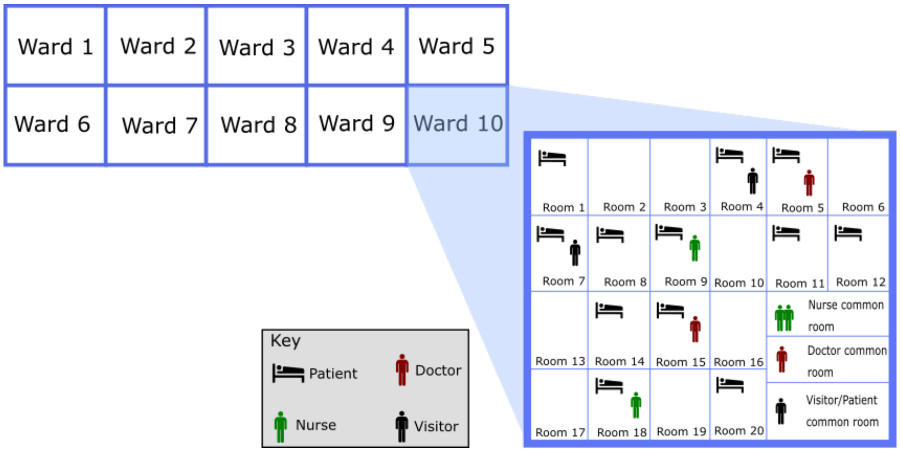


Figure 3: Layout of agent-based model

Visitor agent logic

On each day in the simulation, there is a probability that a patient receives up to two visitors. Visitors do not interact with other patients or healthcare workers in the hospital. Visitors can become transiently exposed and contagious with *C. difficile* through interactions with the patient they are visiting and with contaminated environments. The probability of visitor exposure to *C. difficile* in a patient room increases with the visit duration and depends on the transfer efficiency between surfaces. Visitors can wash their hands upon exit from the patient room according to hand hygiene recommendations regardless of VCPs use. Visitors exit the hospital through a ward common room, which they contaminated with probability dependent on their length of stay in the common room. The baseline model assumed that visitors remain in the common room for five minutes before exiting. Each ward common room may also be used by patients staying within the same ward. Therefore, a patient may become exposed to *C. difficile* through a common area contaminated by a visitor. Environment to agent

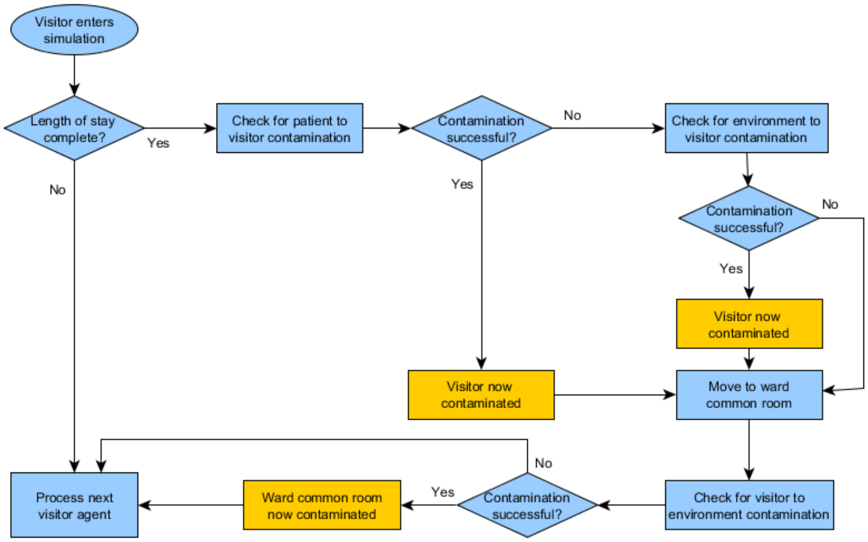


Figure 4: Visitor agent flow logic in the agent based model

contamination is possible through high-touch surfaces, which represent a portion of the room. Common rooms may be cleaned daily, depending on compliance with the bleach cleaning intervention. We assumed that visitors are healthy adults who are not colonized or diseased with *C. difficile*. Therefore, visitors cannot shed *C. difficile*, but can expose and contaminate the environment. Figure 4 shows the logic governing visitor actions in the simulation and section A.2 of the supplement further describes visitor agent logic.

Simulated Interventions

The model includes the following core infection control interventions: nurse and physician hand hygiene, nurse and physician contact precautions, daily environmental cleaning, terminal environmental cleaning, visitor hand hygiene, visitor contact precautions, patient hand hygiene, and *C. difficile* surveillance screening at admission. All interventions were implemented at three increasing levels of compliance: baseline, enhanced, and ideal. The baseline level corresponds to typical compliance with minimal institutional support, or for the surveillance intervention, no asymptomatic screening at admission. Enhanced and ideal implementation represent increasing levels of institutional support. Assumptions of baseline, enhanced, and ideal compliance for the core infection control interventions were derived from literature (eTable A2). Parameters representing high-risk antibiotic use in the hospital remain constant for all interventions and are only changed when explicitly examined by the experiments.

Simulation Settings and Outcomes

We simulated *C. difficile* transmission at a generic 200-bed hospital for 13 months, including a one-month warmup period. Data were collected during the following 12 simulated months. The primary output was the HO-CDI rate, calculated as the number of HO-CDI diagnoses made per 10,000 patient days. Following the CDC's definition, a CDI was classified as hospital onset if it was detected more than three days after admission [11]. CDIs detected within three days of admission were classified as community-onset.

Simulation Scenarios

We conducted 10 sets of simulation experiments to test the value of VCPs in different hospital settings under a variety of infection control implementation strategies. These experiments tested parameter assumptions related to: community distribution of CDI and susceptibility to infection, compliance of healthcare workers with hand hygiene protocols, *C. difficile* transmission from visitors, number of visitors in the hospital, compliance of visitors with hand hygiene protocols, compliance with other infection control interventions, the discrete time Markov chain representing patient disease state transitions, healthcare worker distribution and behavior, and timing of patient arrivals (Table

3). The 10 experiment sets also include one defined a posteriori which considered the "worst case" hospital using parameters from analogous experiments most conducive to infection transmission. Baseline assumptions for the experiments are provided in eTable A2. Individual experiments are described in detail in Table 3. In all the experiments, we compared two scenarios: VCPs de-implemented (i.e., no usage of VCPs) vs. VCPs implemented at an ideal level of compliance (93.5%) to estimate the maximum possible association between VCPs and HO-CDI. All interventions that were not assessed in the simulation scenario were implemented at their baseline level.

We then estimated the minimum required improvement in compliance from baseline that the healthcare worker hand hygiene, daily cleaning, and terminal cleaning interventions would need to achieve a similar or greater association with HO-CDI reduction compared to ideal implementation of the VCPs intervention.

Table 3: Modeled experiment scenarios

Experiment Number	**Description**
0: Base case	
0	Base case: All model baseline parameters, VCPs are deimplemented
1: Patient Composition: varied proportion of susceptible, colonized, and infected patients at admission	
1a	Higher susceptible population: Proportion of nonsusceptible patients at admission decreased from 60% to 0%.

Table 3 continued from previous page

Experiment Number	**Description**
1b	Higher colonization rates: Increased proportion of colonized patients at admission from 6% to 12%
1c	Higher infection rates: Increased proportion of infected patients at admission from 0.3% to 0.6%
1d	Higher at-risk population: Employed all changes in Scenarios 1a-1c simultaneously.
1e	Lower colonization rates: Decreased the proportion of colonized patients at admission from 6% to 3%
1f	Lower infection rates: Decreased the proportion of infected patients at admission from 0.3% to 0.15%
2: HCW Hand Hygiene: varied nursing and physician hand hygiene compliance when caring for CDI and non-CDI patients	
2a	Lower HCW Hand Hygiene: Decreased HCW hand hygiene compliance with non-CDI patients (60% to 30%, nurses; 50% to 25%, physicians) and CDI patients (69% to 34.5%, nurses; 62% to 30.5%, physicians).

Table 3 continued from previous page

Experiment Number	**Description**
2b	Enhanced HCW Hand Hygiene: Increased HCW hand hygiene compliance to reflect enhanced level intervention implementation: non-CDI patients (60% to 79%, nursing; 50% to 71%, physicians) and CDI patients (69% to 84%, nurses; 62% to 77%, physicians).
2c	Ideal HCW Hand Hygiene: Increased HCW hand hygiene compliance to reflect ideal level intervention implementation: non-CDI patients (60% to 96%, nurses; 50% to 91%, physicians) and CDI patients (69% to 97%, nurses; 62% to 93%, physicians).
3: Transmission from visitors: varied the rate at which visitors interacted with the environment.	
3	Higher transmission from visitors: increased the rate of contact between visitors and the common room environment from 0.179 to the patient to common room environment rate of 0.358.
4: Number of visitors in hospital: varied the proportion of patients with visitors, average number of visitors a patient receives, and length of time visitors spend in the hospital.	

Table 3 continued from previous page

Experiment Number	**Description**
4a	Higher number of visitors: increased the average number of visitors a patient receives per day from 2 to 5.
4b	Visitors stay longer in patient room: increased the mean amount of time visitors stay in patient rooms from 15 to 30 minutes.
4c	More patients have visitors: increased the daily probability of having visitors from 0.5 to 1 for each patient
5: Visitor hand hygiene experiments: varied visitor hand hygiene compliance with CDI and non-CDI patients.	
5a	Lower visitor hand hygiene: Decreased visitor hand hygiene compliance with non-CDI patients (35% to 17.5%) and CDI patients (50% to 25%).
5b	Enhanced visitor hand hygiene: Increased visitor hand hygiene compliance to reflect enhanced level intervention implementation: non-CDI (35% to 50%) and CDI patients (50% to 65%).
5c	Ideal visitor hand hygiene: Increased HCW hand hygiene compliance to reflect ideal level intervention implementation: non-CDI (35% to 84%) and CDI patients (50% to 88%).

Table 3 continued from previous page

Experiment Number	Description
6: Intervention fidelity: varied compliance to 5 infection control practices, including daily cleaning, terminal cleaning, limiting the use of fluoroquinolones, limiting the use of high-risk antibiotics, and patient hand hygiene.	
6a	Lower daily cleaning: Decreased proportion of CDI patient rooms and common rooms cleaned daily with bleach from 46% to 23%
6b	Lower terminal cleaning: Decreased proportion of patient rooms cleaned with bleach after patient discharge from 47% to 23.5%
6c	Higher fluoroquinolone use: Increased proportion of patients receiving fluoroquinolones from 7.5% to 15%
6d	Higher high-risk antibiotic use: Increased proportion of patients receiving other non-fluoroquinolone high risk antibiotics from 12.5% to 23%
6e	Lower patient hand hygiene: Decreased patient hand hygiene compliance with non-CDI (33% to 16.5%) and CDI patients (48% to 24%).

Table 3 continued from previous page

Experiment Number	**Description**
7: Patient Disease Transition Probability Matrix: varied the Discrete-time Markov chain underpinning the model between 10 matrices that reflect heterogeneity in CDI progression in humans. (see Codella, et al for further details)15	
7a	Using Matrix 1
7b	Using Matrix 2
7c	Using Matrix 3
7d	Using Matrix 4
7e	Using Matrix 5
7f	Using Matrix 6
7g	Using Matrix 7 (same as base case)
7h	Using Matrix 8
7i	Using Matrix 9
7j	Using Matrix 10
8: HCW Distribution and Behavior: varied the number of HCWs, average time they spend with patients, and number of contacts between patients and HCWs.	
8a	Increased nurse staffing: Increased nurses per ward from 4 to 8

Table 3 continued from previous page

Experiment Number	**Description**
8b	Increased physician staffing: Increased physicians per ward from 2 to 4
8c	Decreased nurse staffing: Decreased nurses per ward from 4 to 3
8d	Decreased physician staffing: Decreased physicians per ward from 2 to 1
8e	Increased nursing visits: Increased nursing visits per patient from 5 to 10
8f	Increased physician visits: Increased physician visits per patient from 1 to 2
8g	Decreased nursing visits: Decreased nursing visits per patient from 5 to 3
8h	Increased length of nurse visits: Changed the average amount of time nurses spend with each patient from 4.65 to 9.3 minutes
8i	Increased length of physician visits: Changed the average amount of time physicians spend with each patient from 10.75 to 21.5 minutes

Table 3 continued from previous page

Experiment Number	**Description**
8j	Decrease length of nurse visits: Changed the average amount of time nurses spend with each patient from 4.65 to 2.325 minutes
8k	Decrease length of physician visits: Changed the average amount of time physicians spend with each patient from 10.75 to 5.375 minutes
8l	Increase probability of patient and nurse contact: Changed probability of contact between patients and nurses from the baseline of 0.358 to 0.588 for 4.7 minutes
8m	Increase probability of patient and physician contact: Changed the probability of contact between patients and physicians from 0.688 to 0.903 for 10.8 minutes
8n	Decrease probability of patient and nurse contact: Changed the probability of contact between patients and nurses from 0.358 to 0.197 for 4.7 minutes
8o	Decrease probability of patient and physician contact: Changed the probability of contact between patients and physicians from 0.688 to 0.441 for 10.8 minutes

Table 3 continued from previous page

Experiment Number	**Description**
9: Patient arrival: Experiments varied the daily rate at which patients are admitted to the hospital.	
9a	Increase patient arrival rate: Increased rate of patient arrivals from the 26 to 52 patients per day
9b	Decrease patient arrival rate: Decreased rate of patient arrivals from the 26 to 13 patients per day
10: Worst-case Scenario, defined a posteriori: Given the results of the preceding experiments, this experiment was designed to obtain the maximum possible effect of VCPs on HO-CDI.	

Table 3 continued from previous page

Experiment Number	**Description**
	This scenario included: a higher at-risk population at admission (Exp 1d), lower HCW Hand Hygiene compliance (Exp 2a), transmission from visitors to the environment modeled as high as colonized patients (Exp 3), an increased number of patients with visitors (Exp 4c), lower visitor hand hygiene compliance (Exp 5a), lower terminal cleaning compliance (Exp 6b), Matrix 10 employed as the underlying Discrete-time Markov chain (Exp 7j), fewer total nurses (Exp 8c), increased number and length of nurse and physician visits (Exps 8e, 8f, 8h, 8i), increased probability of contact between patients and healthcare workers (Exps 8l, 8m), and increased rate of new patient arrivals (Exp 9a).

Statistical Analysis

We ran 5000 replications for each scenario described below to obtain stable estimates. Averages and 95% confidence intervals were calculated for all experiments. We used the SciPy stats package to build confidence intervals with the Python programming language. We considered the association of VCP and HO-CDI to be negligible if the difference between the control and experimental averages were less than one percent.

IRB Approval and Reporting

This study has been approved by the University of Wisconsin Health Sciences Institutional Review Board and follows the CHEERS reporting guidelines.

3.3 Results

The overall baseline rate of HO-CDI when all model input parameters are set at baseline and VCPs are deimplemented was 7.94 (95% CI: [7.91, 7.98]) per 10,000 patient days. This changed to 7.97 (95% CI: [7.93, 8.01]) per 10,000 patient days with VCPs implemented at the ideal level (Scenario 0 in Table 2). The relationship between VCPs and HO-CDI rates followed expected trends (Table 4). For example, an increased proportion of susceptible patients, lower HCW hand hygiene compliance, and lower environmental cleaning compliance was associated with higher estimates of HO-CDI. Across all experiments, VCPs was responsible for a less than 1% change in HO-CDI (Table 2). The experiments varying the proportion of susceptible, colonized, and infected patients at admission, which corresponds to assumptions regarding the prevalence of CDI in the community, showed that the association between VCPs and HO-CDI was negligible across all admission populations. The reduction in HO-CDI rates was less than 1% even under the worst-case scenario (Scenario 10).

The experiments with the largest changes in baseline HO-CDI rate were related to patient disease states (Experiment set 1) and high-impact interventions, such as healthcare worker hand hygiene (Experiment 6a) and daily cleaning (Experiment 2a). Experiment sets 4 and 5, which changed the distribution and behavior of patients in the simulation, had <1% effect on the overall baseline HO-CDI rate of 7.94 per 10,000 patient days.

Table 4: CDI outcomes of de-implementation vs implementation of VCPs, by experiment

Experiment Number	Description	VCPs de-implemented HO-CDI/ 10,000 patient days (95% CI)	VCPs Ideal HO-CDI/ 10,000 patient days (95% CI)	Absolute percent change
0: Base case experiment				
0	Base case	7.94 (7.91, 7.98)	7.97 (7.93, 8.01)	<1%
1: Patient Composition Experiments				
1a	Higher susceptible population	17.18 (17.13, 17.24)	17.19 (17.14, 17.25)	<1%
1b	Higher colonization rates at admission	9.36 (9.32, 9.40)	9.37 (9.33, 9.42)	<1%
1c	Higher infection rates at admission	7.97 (7.93, 8.00)	7.98 (7.94, 8.02)	<1%
1d	Higher at-risk population at admission	18.35 (18.29, 18.40)	18.36 (18.31, 18.42)	<1%
1e	Lower colonization rates at admission	6.78 (6.75, 6.82)	6.79 (6.76, 6.83)	<1%

Table 4 continued from previous page

Experiment Number	Description	VCPs de-implemented HO-CDI/ 10,000 patient days (95% CI)	VCPs Ideal HO-CDI/ 10,000 patient days (95% CI)	Absolute percent change
1f	Lower infection rates at admission	7.91 (7.88, 7.95)	7.91 (7.87, 7.95)	<1%
2: Healthcare Worker Hand Hygiene Experiments				
2a	Lower HCW Hand Hygiene	14.43 (14.38, 14.48)	14.43 (14.38, 14.48)	<1%
2b	Enhanced HCW Hand Hygiene	5.31 (5.28, 5.34)	5.32 (5.29, 5.35)	<1%
2c	Ideal HCW Hand Hygiene:	3.84 (3.81, 3.87)	3.84 (3.81, 3.86)	<1%
3: Double the rate of transmission from visitors to environment		7.93 (7.90, 7.97)	7.95 (7.92, 7.99)	<1%
4: Number of visitors in hospital experiments				
4a	Higher number of visitors	7.94 (7.90, 7.98)	7.97 (7.93, 8.01)	<1%
4b	Visitors stay longer	7.93 (7.89, 7.97)	7.93 (7.89, 7.97)	<1%
4c	More patients have visitors	7.97 (7.93, 8.00)	7.94 (7.9, 7.98)	<1%
5: Visitor hand hygiene experiments				

Table 4 continued from previous page

Experiment Number	Description	VCPs de-implemented HO-CDI/ 10,000 patient days (95% CI)	VCPs Ideal HO-CDI/ 10,000 patient days (95% CI)	Absolute percent change
5a	Lower visitor hand hygiene	7.96 (7.92, 7.99)	7.96 (7.92, 8)	<1%
5b	Enhanced visitor hand hygiene	7.94 (7.90, 7.98)	7.95 (7.92, 7.99)	<1%
5c	Ideal visitor hand hygiene	7.96 (7.93, 8.00)	7.97 (7.93, 8)	<1%
6: Intervention fidelity				
6a	Lower daily cleaning	11.32 (11.28, 11.37)	11.34 (11.3, 11.39)	<1%
6b	Lower terminal cleaning	8.30 (8.27, 8.34)	8.28 (8.25, 8.32)	<1%
6c	Higher fluoroquinolone use	8.43 (8.40, 8.47)	8.43 (8.39, 8.47)	<1%
6d	Higher high-risk antibiotic use	8.83 (8.79, 8.87)	8.85 (8.81, 8.89)	<1%
6e	Lower patient hand hygiene	8.54 (8.50, 8.58)	8.51 (8.47, 8.55)	<1%
7: Patient Disease Transition Probability Matrix				
7a	Using Matrix 1	9.12 (9.07, 9.16)	9.1 (9.06, 9.14)	<1%
7b	Using Matrix 2	6.75 (6.71, 6.78)	6.76 (6.72, 6.79)	<1%
7c	Using Matrix 3	9.06 (9.02, 9.10)	9.07 (9.03, 9.11)	<1%
7d	Using Matrix 4	7.95, (7.92, 7.99)	7.95 (7.91, 7.99)	<1%

Table 4 continued from previous page

Experiment Number	Description	VCPs de-implemented HO-CDI/ 10,000 patient days (95% CI)	VCPs Ideal HO-CDI/ 10,000 patient days (95% CI)	Absolute percent change
7e	Using Matrix 5	8.81 (8.77, 8.85)	8.82 (8.78, 8.86)	<1%
7f	Using Matrix 6	6.76 (6.73, 6.80)	6.77 (6.73, 6.8)	<1%
7g	Using Matrix 7	7.94 (7.91, 7.98)	7.97 (7.93, 8.01)	<1%
7h	Using Matrix 8	5.55 (5.52, 5.58)	5.56 (5.53, 5.59)	<1%
7i	Using Matrix 9	7.87 (7.83, 7.91)	7.85 (7.82, 7.89)	<1%
7j	Using Matrix 10	9.15 (9.11, 9.19)	9.15 (9.11, 9.19)	<1%
8: Healthcare Worker Distribution and Behavior				
8a	Increases number of nurses	8.18 (8.14, 8.22)	8.18 (8.14, 8.22)	<1%
8b	Increases number of physicians	7.54 (7.50, 7.58)	7.53 (7.5, 7.57)	<1%
8c	Decrease number of nurses	7.53 (7.49, 7.57)	7.5 (7.46, 7.54)	<1%
8d	Decrease number of physicians	7.98 (7.94, 8.01)	7.99 (7.95, 8.02)	<1%
8e	Increases number of nurse visits	11.52 (11.47, 11.56)	11.53 (11.48, 11.57)	<1%
8f	Increases number of physician visits	10.31 (10.26, 10.35)	10.32 (10.28, 10.36)	<1%

Table 4 continued from previous page

Experiment Number	Description	VCPs de-implemented HO-CDI/ 10,000 patient days (95% CI)	VCPs Ideal HO-CDI/ 10,000 patient days (95% CI)	Absolute percent change
8g	Decrease number of nurse visits	5.41 (5.37, 5.44)	5.43 (5.4, 5.46)	<1%
8h	Increase length of nurse visits	10.46 (10.42, 10.5)	10.45 (10.41, 10.5)	<1%
8i	Increase length of physician visits	8.6 (8.56, 8.63)	8.57 (8.53, 8.61)	<1%
8j	Decrease length of nurse visits	5.25 (5.22, 5.28)	5.25 (5.22, 5.28)	<1%
8k	Decrease length of physician visits	7.07 (7.03, 7.1)	7.07 (7.03, 7.1)	<1%
8l	Increase rate of patient and nurse contact	16.55 (16.5, 16.61)	16.57 (16.51, 16.62)	<1%
8m	Increase rate of patient and physician contact	9.48 (9.44, 9.52)	9.49 (9.44, 9.53)	<1%
8n	Decrease rate of patient and nurse contact	16.21 (16.16, 16.27)	16.21 (16.16, 16.27)	<1%

Table 4 continued from previous page

Experiment Number	Description	VCPs de-implemented HO-CDI/ 10,000 patient days (95% CI)	VCPs Ideal HO-CDI/ 10,000 patient days (95% CI)	Absolute percent change
8o	Decrease rate of patient and physician contact	9.45 (9.41, 9.49)	9.45 (9.41, 9.49)	<1%
9: Patient arrival				
9a	Increase patient arrival rate	8.22 (8.19, 8.25)	8.22 (8.18, 8.25)	<1%
9b	Decrease patient arrival rate	5.86 (5.81, 5.9)	5.87 (5.82, 5.91)	<1%
10: Worst-case scenario				
10 (Worst Case)	Conditions from experiments: 1d, 2a, 3, 4c, 4b, 5a, 6a, 6b, 6c, 6d, 6e, 7j, 8c, 8e, 8f, 8h, 8i, 8l, 8m, 9a	128.76 (128.65, 128.86)	128.79 (128.68, 128.90)	<1%

Table 5 summarizes the results of incremental improvement experiments that increased average compliance of hand hygiene of healthcare workers from a baseline estimate of 55% to 56% (60% to 61% for nurses; 50% to 51% for physicians) and compliance to environmental cleaning from 47% to 49% (46% to 47% for daily cleaning; 47% to 50% for terminal cleaning). For healthcare worker hand hygiene and environmental cleaning, no more than 3% improvements in compliance was associated with greater CDI reduction than ideal VCPs implementation.

Table 5: Changes in hand hygiene and cleaning compliance required to achieve reduction in HO-CDI/10,000 patient days on par with that of VCPs ideal intervention

Intervention	Baseline		Improved		Percent reduction in HO-CDI rate
	Compliance (%)	HO-CDI/10,000 Patient days	Compliance (%)	HO-CDI/10,000 Patient days	
Visitor contact precautions	50	7.98 (7.94, 8.01)	93.5	7.97 (7.93, 8.01)	<1%
Nurse hand hygiene	60		61	7.82 (7.78, 7.86)	2.01%
Physician hand hygiene	50		51	7.90 (7.86, 7.94)	1.00%
Daily cleaning	46		47	7.86 (7.82, 7.90)	1.50%
Terminal cleaning	47		50	7.88 (7.84, 7.92)	1.25%

3.4 Discussion

To our knowledge, this is the first study to estimate the association of VCPs and HO-CDI rates. This modeling study suggests that the contribution of VCPs to overall HO-CDI rate is negligible and similar benefits could easily be obtained by increasing compliance to core infection control interventions such as healthcare worker hand hygiene or environmental cleaning. The simulation results were not associated with a major reduction in HO-CDI via VCP use in any of the examined hospital configurations or patient profiles. The adaptability of this model enables these experiments to be run for different hospital configurations and can help estimate the association between VCPs and HO-CDI in specific settings. As no previous study has evaluated the contributions of VCPs to HO-CDI, direct comparison to previous studies is not possible. However, multiple studies have described the harms of contact precautions for patients. Previous studies reported increased delirium and depression associated with contact precautions [75–77]). Patients under contact precautions also reported lower care satisfaction [78]. It is likely that these negative effects are worsened under VCPs [72].

Other studies have questioned the effectiveness of VCPs for MRSA and VRE. The 2015 SHEA report states that the high prevalence of MRSA and VRE in the community make VCPs an ineffective intervention [65]. As community spread is increasingly recognized as a source of *C. difficile*, with some studies noting a general increase in community onset CDI since the early 1990's, a similar effect may explain the potential low impact of VCPs [1]. The SHEA guidelines also suggest that visitor behavior, particularly that visitors normally do not interact with multiple patients, may be a reason why this intervention is associated with little HO-CDI reduction.

High fidelity and sustained implementation of VCPs requires considerable resources. The SHEA guidelines cite the difficulty of educating visitors and enforcing compliance with contact precaution practices as reasons against the use of contact precautions among visitors of MRSA and VRE patients. These reasons likely generalize to *C. difficile*, as the recommended gown, gloves, and visitor education for MRSA and VRE are similar to that of CDI.

Our findings have important implications for healthcare institutions, infection prevention programs, and clinicians. The minimal changes to baseline HO-CDI rate with VCPs show that any restrictions regarding visitor length of stay or number of visitors allowed may likely be relaxed with minimal change in HO-CDI rates. Removing VCPs for CDI control would also decrease the HCW burden associated with enforcing and managing compliance to VCPs, allowing additional time and effort to be allocated toward more effective interventions [79–81]. These include HCW hand hygiene and environmental cleaning, which have consistently been linked to significant decreases in HO-CDI [82–84].

The personal protective equipment (PPE) resources saved by removing VCPs can also be used to improve PPE inventory for use during acute infectious outbreaks. For example, in the coronavirus disease 2019 (COVID-19) outbreak, guaranteeing PPE to health professionals became a major challenge with calls for removing contact precautions for MRSA and VRE patients during the pandemic [85, 86]. Minimizing PPE use among visitors to CDI patient rooms would provide much needed additional resources for HCWs, at seemingly minimal risks for worsening *C. difficile* transmission.

Our study has several limitations. First, all data analyzed in this study was generated through simulation and not through clinical experiments. Therefore, any conclusions drawn from this study should at most be used to influence the purpose or design of such clinical experiments. Second, we did not consider the effect of community-onset CDI on hospital visitors. Our model assumed that visitors could not be infected or colonized, thus, visitors were not able to expose patients to *C. difficile* spores from the community. Our study does not consider what benefit VCPs may give to visitors. The model also simulated each ward uniformly and did not account for differential CDI risk across wards. We also did not consider how the use or de-implementation of VCPs may affect compliance with other infection control measures, such as hand hygiene or healthcare worker contact precautions. It is possible that de-implementing VCPs would suggest to visitors and healthcare workers a diminished risk of *C. difficile*, which could in turn decrease compliance to other infection control practices that are highly effective against HO-CDI. A recent study of healthcare workers found that the use of contact precautions was associated with increased risk-mitigating behavior, such as improved hand hygiene [87]. However, another study suggests that a threshold of patients designated under isolation exists at which compliance to contact precautions decreases [19]. These studies suggest interactions between infection control interventions and their perceived importance; further work is required to understand if such an effect could be present upon de-implementation of VCPs for CDI patients. This study also did not examine the impact of VCPs in a pediatric setting, where visitor-patient interactions greatly differ from the adult, acute care hospital setting. However, our group's prior agent-based model of pediatric hospital *C. difficile* transmission showed little reduction in HO-CDI with VCPs implemented at an ideal level under baseline assumptions [88]. Further research is required to estimate the contribution of VCPs in a pediatric care setting under different configurations. Finally, our assumption that visitors can only contaminate the environment, but not healthcare workers or other patients, may be a limitation. However, given that most visitors do not physically interact with more than one patient, it is unlikely that changing this assumption would greatly affect the current model outcomes.

In conclusion, VCPs were found to have a minimal association with HO-CDI rates in this model. In the context of these findings and financial and supply chain constraints, the infection control community should reevaluate the value of VCPs for patients with CDI. If this model is correct, removing this intervention with minimal association with HO-CDI rates from prevention bundles would allow better allocation of resources for containment.

Chapter 4

Validating agent-based simulation model of hospital-associated *Clostridioides difficile* infection using primary hospital data

4.1 Introduction

Agent-based simulation models (ABMs) have been increasingly used to model infectious diseases. Although ABMs may overcome major limitations of conventional modeling approaches such as state-transition models and discrete-event simulation, their applicability is limited because of their extensive data needs [89]. ABMs need large amounts of data not only for estimating model parameters such as those related to agent interactions, but also for conducting validation.

The ISPOR-SMDM Modeling Good Research Practices Task Force notes the success of healthcare models depends on trust and confidence, which could be achieved via transparency and validation [90]. However, creating and validating complex ABMs can be especially difficult because of limited available primary historical data. While several ABMs of healthcare settings exist, few have been validated using primary data from an extant system: often, validation efforts use community- or national-level historical data [91–95]. When primary historical data is used in the model validation process, it is typically used to calibrate certain model parameters and therefore does not serve as an external validator [94, 96]. Unvalidated, generic models may not be able to fully represent a specific hospital's characteristics and therefore may be of diminished utility in decision making. Challenges associated with validation posed by insufficient data are amplified when modeling specific hospitals because primary hospital data can be particularly scarce. Therefore, approaches to validating ABMs of specific healthcare settings likely need to incorporate both primary data as well as data from literature. There is currently a dearth of formalized procedures that explore possibilities for blending literature and primary data sources to contribute to model validation.

Additionally, ABMs depend heavily on the networks facilitating interactions between agents and their environment, yet validating socio-environmental networks is especially challenging. For example, ABMs may record the frequency of interactions among agents in a system (e.g., patients to patients, or patients to healthcare workers) that contribute to the transmission of a disease, but there is paucity of data and methods to validate these frequencies and the overall socio-environmental network structure. As a result, modelers might need to consider indirect metrics of network behavior to validate socio-environmental networks, such as emergent network effects, but to the best of our knowledge this approach has not been employed in the context of modeling disease transmission in a hospital setting.

To this end, this study demonstrates how an ABM and its associated socio-environmental network structure could be externally validated using primary hospital data and novel risk factors. For this purpose, we use a previously developed ABM of hospital-associated *Clostridioides difficile* infection (*C. difficile*; CDI), a gastrointestinal infection associated with abdominal pain, diarrhea, and death in severe cases. Using specific characteristics from a 426-bed academic hospital in the Midwestern United States, we adapt the previously developed generic model to the target academic hospital-specific setting. Adapting a generic ABM to a specific hospital environment is not an insignificant task, as thorough validation requires investment in rigorous data gathering, and the benefit of this undertaking is unclear. Thus, to assess the benefit of hospital-specific modeling, we compare the relative effectiveness of different infection control interventions across the generic and hospital-specific models. These experiments are intended to demonstrate the value of hospital-specific modeling, and support arguments in favor of greater deliberation in model building and validation.

4.2 Methods

4.2.1 CDI Background

CDI is one of the most common healthcare-associated infections in the United States and primarily spreads via the fecal-oral route through infectious spores shed in the stool of infected patients [1, 4]. Removal of these spores from hard surfaces or hands requires the use of strong sporicidal agents or vigorous soap and water cleansing, respectively. CDI susceptibility can vary, with risk factors including advanced age, immunosuppression, and antibiotic exposure [2]. Healthcare facilities differentiate between CDIs likely developed in the hospital or the community, referring to cases as hospital-associated CDI (HA-CDIs) or community-associated CDI (CA-CDI), respectively [97].

To limit the prevalence of CDI in hospitals, infection control programs develop and deploy interventions, with varying costs and effectiveness, aimed at eliminating *C. difficile* spores. Infectious disease control guidelines recommend several interventions, including increased hand hygiene, environmental cleaning, and testing/screening at patient admission, among others [4].

4.2.2 Overview of the existing agent-based simulation model developed for a generic hospital setting

Barker, et al and Codella, et al previously developed an ABM of CDI spread in a generic hospital [20, 94]. The ABM includes four types of agents: patients, nurses, doctors, and visitors. Patients interact with the environment and other agents during their stay, and each interaction may propagate infection with a probability dependent on the infection control interventions in place. All patients that test positive for CDI start a 14-day course of antibiotics and extend their length of stay by approximately 2.3 days [98, 99]. At the end of a stay, the patient is discharged, and the agent is removed from the model. In accordance with typical hospital protocols, patients with known CDI infections may be discharged even if they have not completed their course of antibiotics. Appendix A contains behavior logic flow diagrams for all agent types in the ABM.

In this model, patients are the only agents that may develop CDI and shed infectious spores, while healthcare worker and visitor agents may become transiently contaminated. Patient CDI state is modeled using a discrete-time Markov chain updated every 6 hours in-simulation with nine states: susceptible, exposed, colonized, infected, recurrent colonized, recurrent infected, cleared, dead, and non-susceptible. Patients may only transition into the “exposed” state if they encounter *C. difficile* spores. Patients

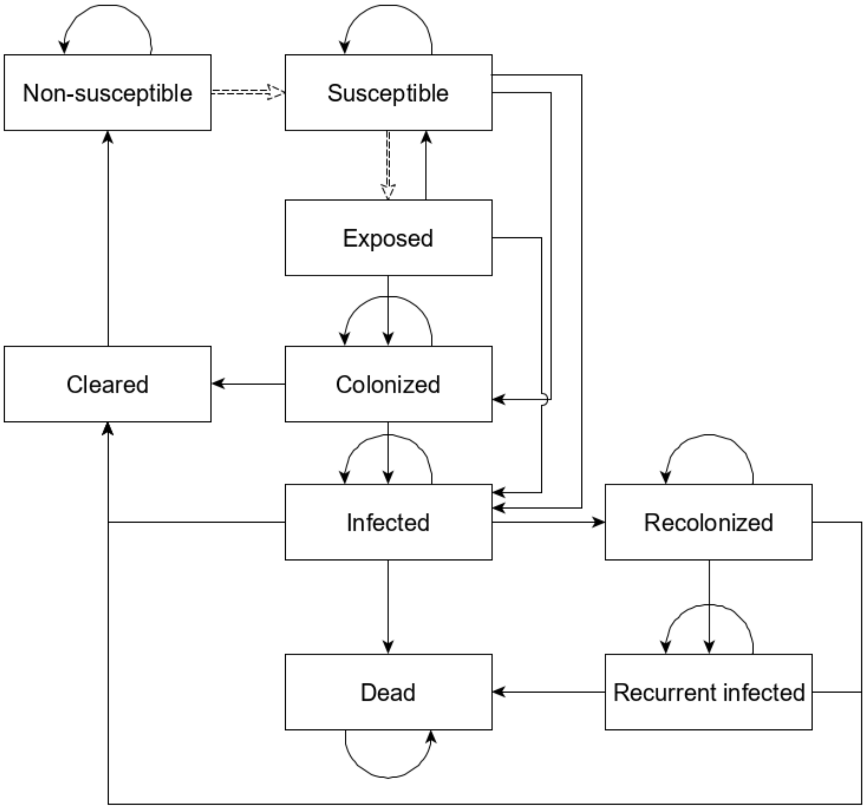


Figure 5: Discrete-time Markov chain structure representing the progression of CDI in an individual patient

may only transition from the "non-susceptible" to "susceptible" states if they begin a course of a high-risk antibiotics. All other disease state transitions are determined using the transition probability matrix. Figure 5 visualizes this discrete-time Markov chain, with the dashed arrows representing infection control dependent transitions. The discrete-time Markov chain transition probability matrix was calibrated using long term probabilities estimated from literature and hospital data [94].

To reduce variability and compare results across different conditions, the model uses common random numbers generated by the Colt Project's Mersenne Twister algorithm

[100]. The ABM was developed in the Java programming language using Microsoft's Visual Studio editor. Each set of 5000 replications of the ABM required roughly one hour on a single desktop computer with an Intel Core i5-8500 CPU and 16GB RAM. Further details of the generic ABM are available in previous publications [20, 63, 94].

4.2.3 Adapting the generic hospital ABM to target hospital setting

The H-ABM simulates CDI-related events in 426 single occupant patient rooms of a Midwestern academic hospital. Patient rooms are organized into 18 wards of varying size according to the target hospital layout. We included an additional space representing the hospital cafeteria, which healthcare workers may visit once per shift when not interacting with patients. The H-ABM also includes common room spaces for patients/visitors and healthcare workers within each ward. In this model, we assume that nurses see patients within a single ward and use only the common rooms in that ward, while doctors consult for patients across the hospital and use common rooms across multiple wards. Figure 6 illustrates the modeled layout of the target hospital.

We focused on replicating CDI-related trends between years 2013 and 2018 for which the most complete data on interventions and infections are available, as described in Appendix B. Appendix C provides a detailed description of the major changes between H-ABM and the ABM representing a generic hospital. Appendix Tables C1 and C2 provide further parameters governing agent behavior and environmental conditions in H-ABM.

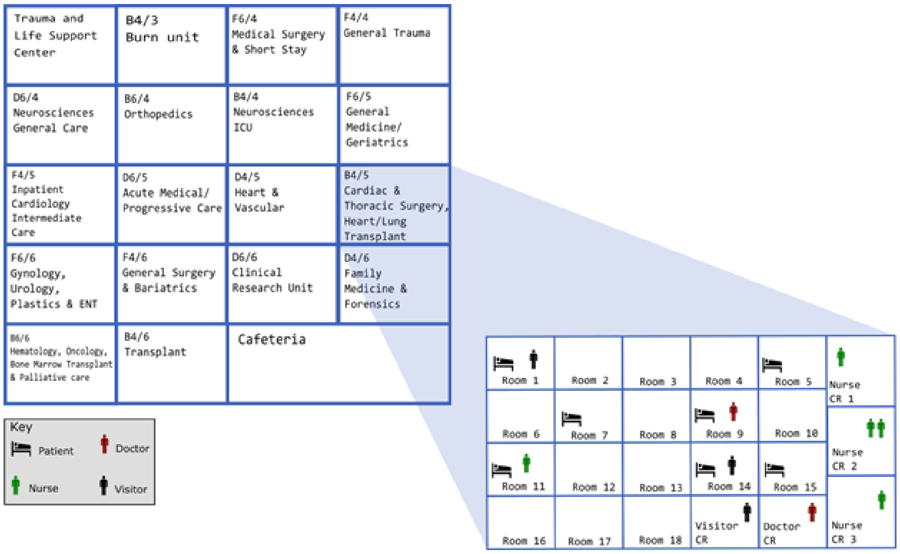


Figure 6: Layout of the hospital simulated in H-ABM

4.2.4 Modeling infection control interventions

The H-ABM included several infection control interventions: nurse and doctor hand hygiene, nurse and doctor contact precautions, daily environmental cleaning, terminal environmental cleaning, visitor hand hygiene, visitor contact precautions, patient hand hygiene, patient transfer, and *C. difficile* screening at admission. To simulate the HA-CDI rate for the years 2013-2018, compliance and effectiveness were estimated for each intervention. We define "compliance" as the proportion of agents following infection control protocol in a single opportunity, and "effectiveness" as the probability that each infection control event successfully eliminates or blocks transmission of *C. difficile*. Several parameter estimates varied for CDI and non-CDI patient rooms. Further details of infection control interventions are provided in Appendix D.

4.2.5 Parameter estimation and data sources

Several parameters in our model were estimated from primary hospital data. To estimate the proportion of susceptible patients by ward, we used hospital admission data to determine the number of patients aged 65 years or older, or who had been taking antibiotics upon admission. We also assumed that all patients admitted to wards specialized in caring for high-risk classes of patients (e.g., solid organ transplant) are susceptible to CDI. High risk wards were identified by a clinical expert on CDI in the target hospital. We also used hospital administrative data to estimate the daily patient arrival rate, antibiotic use by ward, and average base length of stay by ward. The proportion of susceptible patients and the antibiotic use in the target hospital were assessed for each of the years 2013-2018 to simulate broader trends in antibiotic use during this period in the US [101]. A full description of hospital layout and parameters are included in Table 1, Appendix Tables C1-C4, and Figure 2. Parameters related to CA-CDI, such as the proportion of admitted patients that are colonized or infected, were estimated from literature. Parameters unlikely to vary significantly from the previously published generic ABM, such as the transfer efficiency of *C. difficile* between surfaces, were not changed for the hospital-specific model.

Another crucial input for representing CDI-related events is the use of infection control interventions, which have varying degrees of fidelity over time. We estimated parameters related to interventions using hospital data of monthly observed healthcare worker hand hygiene events from 2013-2018. This data included counts of nurses and doctors performing hand hygiene actions while seeing patients, and the number of hand hygiene events using soap and water or alcohol-based hand rub. We used these counts and the estimated effectiveness of soap and water and alcohol-based hand rub to estimate the overall effectiveness of each hand hygiene event in our model (see Appendix B for additional data descriptions). Because patient and visitor hand hygiene data were not available, we scaled the baseline compliance and effectiveness estimates according to observed healthcare worker hand hygiene compliance and effectiveness. Baseline estimates were derived from the generic model and more recent studies. Parameters for daily and terminal environmental cleaning compliance and effectiveness were also scaled similarly. Appendices B, C, and E provide additional details related to parameter estimation and scaling.

4.2.6 Validation experiments for replicating observed CDI data over time

To test the ability of our model to replicate CDI trends in the target hospital, we ran 5000 replications of the H-ABM for the years 2013-2018 and compared the results to actual HA-CDI data for each year. We used 5000 replications to generate stable outcome estimates with narrow 95% confidence intervals. CDI rates were recorded as the number of hospital-associated cases per 10,000 patient days, consistent with the CDC's standard definition for HA-CDI [102].

4.2.7 Validation of socio-environmental network structure via colonization pressure

Colonization pressure is a measure of infectious pathogen prevalence in a susceptible individual's environment. Multiple studies have already found that patients residing in wards with high CDI prevalence, and therefore high colonization pressure, have increased risk of developing CDI [103,104]. Theoretically, this leads to increased opportunities for *C. difficile* propagation, as more members of the socio-environmental network are likely to be contaminated. For example, healthcare workers within a high colonization pressure socio-environmental network (such as a single hospital ward), can more easily propagate *C. difficile* to non-infected patients, thereby increasing the risk of developing CDI for each patient in their network. Colonization pressure is an example of emergent behavior in the H-ABM, and does not directly determine if a susceptible patient develops CDI during a hospital stay. Thus, an association between colonization pressure and risk of developing CDI serves as a proxy to assess if the socio-environmental networks in H-ABM are reflective of reality. To validate our the modeled socio-environmental networks using colonization pressure, we used the following equation adapted from the study by Dubberke et al. (2007) [103] to calculate the mean colonization pressure (MCP) for each patient agent in every year of the historical simulation.

$$\text{MCP} = \frac{\sum_{LOS} \text{Number of colonized or infected patients in ward, per day}}{\text{Total number of susceptible days}}$$

For each day that a patient was susceptible, the numerator was increased by the number of colonized or infected patients in the same ward. Patients that were known to be colonized or infected with *C. difficile* at some point in their stay were classified as "case" patients. Community-associated colonizations or infections were not considered as case patients. However, community-associated colonizations or infections contributed to the number of colonized or infected patients in their respective wards per day. Any susceptible patients that did not become colonized or infected were considered "non-case."

4.2.8 Impact of infection control interventions on CDI rates in the generic hospital model vs H-ABM

We estimated the effect of hospital-specific characteristics of H-ABM by comparing its impact on HA-CDI with that of the generic hospital ABM (as described in Barker, et al [20]) under similar conditions. We considered three discrete levels of infection control implementation: "baseline," "enhanced," and "ideal" corresponding to increasing levels of compliance and effectiveness parameters. We ran 5000 replications of the H-ABM with a single infection control intervention implemented with the "enhanced" or "ideal" parameters from Barker, et al, with all others implemented at "baseline." To assess the impact of each intervention, we also ran 5000 replications of H-ABM with all interventions' "baseline" parameters. For each experiment we collected the rate of HA-CDIs per 10,000 patient days, as well as the rate of asymptomatic colonizations per 1,000 admissions. Finally, we ranked each of the nine interventions according to their reduction in HA-CDI for both the H-ABM and generic model.

4.2.9 Statistical and sensitivity analysis

For all experiments in this study, we calculated 95% confidence intervals with the SciPy stats package for the Python programming language.23 We conducted a sensitivity analysis on three parameters of interest: the proportion of patients colonized at admission, the proportion infected at admission, and the CDI transition probability matrix.

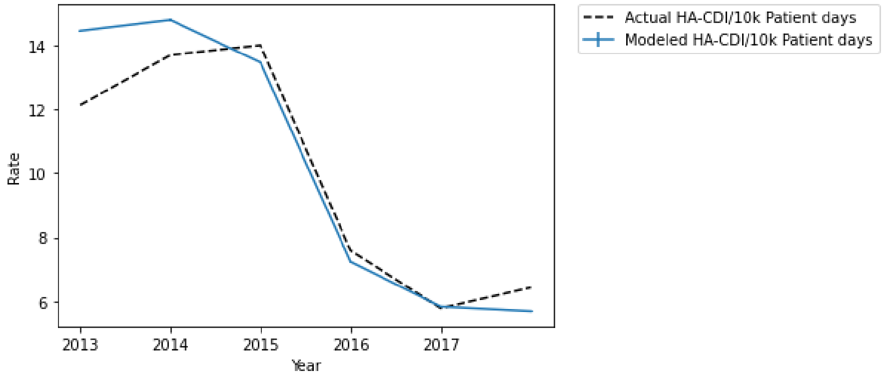


Figure 7: Modeled vs. actual rate of HA-CDI per 10,000 patient days, 2013-2018

4.3 Results

Estimates for model input parameters for 2013-2018 are shown in Table 6. Hospital reported rates of observed healthcare worker hand hygiene compliance were over 80% in all years. To account for this unrealistically high compliance, we assumed that these observed rates of hand hygiene represented the compliance rates when interacting with known CDI patients. The target hospital reported rates of healthcare worker soap and water or alcohol-based hand rub usage were consistent with literature.

Using the estimated hospital and intervention parameters, the model was able to reproduce CDI trends from 2013-2018. Figure 7 shows the rate of HA-CDI per 10,000 patient days as predicted by the simulation with 95% confidence intervals for each yearly estimate and the actual rates by year. Notably, our results show a 46% percent drop in simulated HA-CDI per 10,000 patient days from 2015 to 2016 (13.47 to 7.23), akin to the 46% drop in the historical rate (14.01 to 7.58).

Across all simulated years, the average total number of case and non-case patients was approximately 687 and 91,283, respectively. The average MCP for all patients and

Table 6: Hospital and infection control intervention parameter estimates, by year

Intervention	Year						Source
	2013	2014	2015	2016	2017	2018	
Hand Hygiene Parameters							
Standard Patient							
Healthcare workers compliance (effectiveness)with hand hygiene	67% (34%)	68% (33%)	70% (34%)	80% (34%)	83% (35%)	84% (35%)	[105–109] (HD)
Visitor compliance (effectiveness)with hand hygiene	37% (34%)	37% (33%)	38% (34%)	61% (34%)	69% (35%)	69% (35%)	[105,106,110] ([20])
Patient compliance (effectiveness)with hand hygiene	27% (34%)	27% (33%)	28% (33%)	28% (34%)	28% (35%)	28% (35%)	[111–113] ([20])
CDI Patient							
Healthcare workers compliance (effectiveness)with hand hygiene	86% (84%)	87% (82%)	89% (83%)	89% (84%)	88% (86%)	89% (86%)	HD ([20,114,115])
Visitor compliance (effectiveness)with hand hygiene	61% (81%)	62% (78%)	63% (80%)	76% (80%)	81% (82%)	82% (82%)	[20,105,106,110] ([20,114])
Patient compliance (effectiveness)with hand hygiene	58% (80%)	59% (78%)	60% (80%)	60% (79%)	60% (82%)	61% (82%)	[111–113] ([20,114])
Contact Precautions Parameters							
Healthcare workers compliance (effectiveness)with contact precautions	82% (68%)	83% (66%)	84% (67%)	88% (67%)	90% (69%)	91% (69%)	[114] ([20,116–119])
Visitors compliance (effectiveness)with contact precautions	61% (68%)	62% (66%)	63% (67%)	66% (67%)	66% (69%)	67% (69%)	[114] ([20,116–119])
Environmental Cleaning Parameters							
Standard Patient							
Daily cleaning compliance (effectiveness)	56% (44%)	57% (42%)	58% (43%)	73% (43%)	79% (45%)	79% (44%)	[120–125] ([20])
Terminal cleaning compliance (effectiveness)	56% (98%)	57% (95%)	58% (97%)	90% (100%)	98% (100%)	98% (100%)	[120,126–129] ([20,130])
CDI Patient							
Daily cleaning compliance (effectiveness)	56% (96%)	57% (94%)	58% (96%)	74% (96%)	79% (99%)	79% (98%)	[120–125] ([20])
Terminal cleaning compliance (effectiveness)	57% (100%)	57% (100%)	59% (100%)	92% (100%)	98% (100%)	98% (100%)	[120,126–129] ([20,130])
Admission Parameters							
Proportion of patients who are colonized asymptomatically at admission	6.10%						[20]
Proportion of patients with CDI at admission	0.29%						[20]
Patient arrival rate	72/day						HD
CDI Testing Algorithm Parameters							
Percent of patients with unexplained gastrointestinal symptoms at admission	2%						HD
Percent of patients with possible non-CDI causes of gastrointestinal symptoms after 48 hours	43%						HD

HD = Hospital Data

Table 7: Relative risk of CDI by MCP

Mean Colonization Pressure (MCP) Group	Average Number of Case Patients	Average Number of Non-case Patients	Risk Ratio (95% CI)
0.36	420.7	62411.5	Reference
0.36 - 0.42	20.12	1784.4	1.66 (1.07, 2.60)
0.42	246.4	27087.3	1.35 (1.17, 1.60)

patients without CDI was approximately 0.36. For patients with CDI, the average MCP was approximately 0.42. To further analyze the effect size of colonization pressure, we split the case and non-case population into three subgroups of MCP based on the case and non-case population averages: <0.36, 0.36-0.42, and > 0.42. Approximately 36% of case patients belong to the highest MCP group (> 0.42), vs 30% of non-case patients. Similarly, approximately 61% of case patients belonged to the lowest MCP group (< 0.36), vs 68% of non-case patients. In the H-ABM, greater than average MCP (0.36) was associated with a 37% increase in risk of CDI colonization or infection (Risk ratio: 1.37; 95% CI: [1.17, 1.59]). Analysis of the MCP groups demonstrated that increased MCP was associated with a significant risk of CDI colonization or infection, with patients in higher than average MCP groups having up to 66% increased risk of CDI (Table 7).

Table 8 displays the changes in HA-CDI and asymptomatic colonization rates relative to the baseline implementation for both the H-ABM and the generic model and ranks each of the nine infection control interventions by reduction in HA-CDI rate and asymptomatic colonizations. The baseline rate of HA-CDI per 10,000 patient days was 8.28 and 20.10 for the generic model and H-ABM, respectively. In the experiments conducted by both models, daily cleaning was consistently associated with the largest reduction in HA-CDI and colonization rates. However, screening at admission is less effective when

Table 8: Ranking of infection control interventions (1-9) by percent reduction in HA-CDI per 10,000 patient days, for the H-ABM and the generic model; with 1 representing the greatest reduction and 9 representing the least reduction

Intervention	H-ABM		Generic Model	
	HA-CDI per 10k patient days		HA-CDI per 10k patient days	
	Enhanced	Ideal	Enhanced	Ideal
Daily cleaning	65% (1)	72% (1)	69% (1)	72% (1)
Healthcare worker contact precautions	2% (6)	3% (6)	1% (7)	3% (7)
Healthcare worker hand hygiene	30% (2)	49% (2)	33% (3)	52% (2)
Patient hand hygiene	11% (4)	21% (3)	12% (5)	22% (5)
Patient transfer	0% (7)	0% (7)	4% (6)	5% (6)
Screening at admission	18% (3)	19% (4)	36% (2)	37% (3)
Terminal cleaning	8% (5)	11% (5)	18% (4)	24% (4)
Visitor hand hygiene	0% (7)	0% (7)	0% (8)	0% (8)
Visitor contact precautions	0% (7)	0% (7)	0% (8)	0% (8)

implemented at the enhanced level in the H-ABM than in the generic model, and is associated with a smaller reduction in HA-CDI rates than enhanced healthcare worker hand hygiene. Full HA-CDI and asymptomatic colonization rates by intervention are included in Appendix F.

4.4 Discussion

The H-ABM was able to replicate observed HA-CDI trends from 2013-2018, including the large relative drop in HA-CDI from 2015 to 2016 that most likely resulted from increased use of infection control interventions. Point estimate discrepancies could be due to historical fluctuations in the community prevalence of CDI, in adherence to/effectiveness of infection controls, and in the number of susceptible patients, among several other causes. In particular, the increase in historical HA-CDI rates from 2013-2015 could be the result of many difficult to detect hospital characteristics. One possibility is the transition from institutional definitions of HA-CDI to CDC definitions, and gradual changes in the reporting structure of CDI starting around the year 2012 [131]. Most of these causes are nearly impossible to capture via an ABM and attempting to capture all of them may result in "overfitting," reducing the utility of our model for planning future infection control strategies. To avoid this "overfitting" we focused primarily on representing CDI trends and infection control relative performance. We believe our results provide a useful illustration of the model's ability to assess the relative impact of different infection control interventions used simultaneously.

This study also presents an alternate to common validation methods that rely on the availability of large quantities of outcomes data. Common validation approaches use calibration to estimate unknown parameters and reconcile modeled and actual outcomes of interest. While such methods may be appropriate for systems with vast historical data, this is not feasible for the hospital-specific setting. To overcome this, our validation approach emphasizes incorporating relevant system-specific features into the logic of the model.

Our colonization pressure analysis agrees with the existing literature that demonstrates a significant effect size of MCP in H-ABM. However, our risk ratios for the effect size of MCP differ from literature reporting unadjusted risk ratios ranging from close to 1 to 8.7 for varying levels of colonization pressure [103,104]. The discrepancy of our risk ratios ranging from 1.35-1.66 with those found in literature could be the result of many hospital-related factors. Lower adherence to environmental cleaning for rooms housing CDI patients may lead to increased spore prevalence in wards, resulting in more CDI cases and higher impact of colonization pressure. Other hospital-specific factors, such as the number of double occupant rooms, size of wards, and the distribution susceptible patients and of healthcare workers may have impacted the effect size of MCP in other studies. Our MCP effect size discrepancy may also be the result of simulation-specific factors. In our simulation, we assume that once a patient has been tested, their CDI status is known by all HCWs and patients in the model. In an actual hospital setting, patient CDI status may not always be known ubiquitously, resulting in insufficient infection control practices and an increased effect of colonization pressure as *C. difficile* spore prevalence increases. Additionally, our H-ABM follows strict testing rules independent of known CDI prevalence. Testing in a real hospital may be biased, as clinicians may be more likely to test patients for CDI if another known CDI patient is housed in the same ward. The effect size of colonization pressure is relatively understudied for CDI, but studies examining comparable infections like Methicillin-resistant Staphylococcus aureus and Vancomycin-resistant Enterococcus have found a more similar effect size for the highest colonization pressure group as our H-ABM [132–134].

Experiments examining the single intervention reduction in HA-CDI and asymptomatic colonization rates in the H-ABM and generic model demonstrate the utility of hospital -specific modeling. The change in the relative ranking of high-impact interventions when adapting a generic model to a specific setting suggests that generic models are limited in their applicability to real-world settings. For the many hospitals that need to create infection control strategies under tight budget constraints, the relative ranking of different interventions is especially salient information. As ABMs become increasingly popular in healthcare applications, it is of growing importance to understand the tradeoffs between types of models. While generic models may be simpler to create, they may not capture the nonlinearities that arise from hospital-specific characteristics. Conversely, hospital-specific models may facilitate greater confidence in decision makers, but are more data-intensive and the incremental benefit of hospital-specific model findings against generic model findings is not always clear. The literature on hospital ABMs reveals that both generic and hospital-specific models can produce valuable insights [92–94, 135, 136]. We hope our results may be of use to other modelers as they consider the tradeoff between the flexibility of a generic model and tailored findings of a hospital-specific model. To the best of our knowledge, our experiments are the first to attempt to directly characterize this tradeoff by analyzing two analogous models.

Our H-ABM validation has several limitations. Compliance and effectiveness for environmental cleaning and contact precautions were not directly derived from hospital data and were instead scaled from other intervention data. Extensive data collection efforts would have been consistently required from 2013-2018 to accurately estimate these parameters from hospital data. However, this level of data collection is often infeasible in hospitals. Reliable intervention data would also need to be obtained covertly, thereby increasing data collection costs [111, 137]. Thus, it is necessary to develop more novel methods of estimating unknown parameters using proxies. Our study also does not include any calibration of model parameters, which is uncommon among ABM validation studies. Previously published ABMs of HA-CDI calibrated only the transition probability matrix that governs CDI progression using a large data set and estimates derived from literature [94]. Any additional calibration effort may not be appropriate for this study because the impact of hospital configuration primarily affects the rate at which susceptible patients are exposed to *C. difficile*; an event fully determined by model assumptions and logic. However, sensitivity analyses show that the overall CDI trends from 2013-2018 produced by the H-ABM are consistent across different hospital assumptions, as seen in Appendix G. By focusing on representing historical conditions to the best of our ability, we may consider this study as a type of external validation of the model's logic and assumptions. The performance of the external validation suggests the logic framework of H-ABM could be applicable to other healthcare settings.

Further work is necessary to continue validation of the H-ABM. Comprehensive data for all infection control intervention implementation should be collected for several years with the goal of model validation. Patient heterogeneity and risk factors for CDI, aside from age, admission ward, and antibiotic use, should also be incorporated into the model. To strengthen the validation of social and environmental networks in the model, a supplementary study is needed to determine the effect size of colonization pressure in the target hospital. Despite the need for additional work, this study exemplifies an alternate to typical validation methods and the utility of hospital-specific modeling.

Chapter 5

Reducing hospital associated *Clostridioides difficile* infection: an optimal control approach

5.1 Introduction

The incidence of CDI remains high in the US, and containment has been designated a public health priority by the Centers for Disease Control. Transmission of *C. difficile* occurs primarily in healthcare settings, but prevention remains challenging for several reasons. First, *C. difficile* is transmitted person-to-person as well as environment-to-person, requiring infection controls that can impede *C. difficile* propagation along one or more of these pathways. Second, *C. difficile* spores can live on hard surfaces for several months and are not effectively removed by common alcohol-based hand sanitizers and disinfectants [9, 138]. Because of the challenges in mitigating CDI, hospitals use several infection control interventions with varying effectiveness and resource needs. This leads to the final, and perhaps biggest, challenge to mitigating CDI: hospital infection control programs typically responsible for selecting interventions are often underfunded/understaffed. Therefore, these infection control professionals have a strong imperative to maximize the value of every dollar spent.

Many studies report on the impact of individual infection control interventions or intervention bundles, but it is not clear how to combine infection controls to optimally limit CDI spread in a unique hospital setting. This is crucial because the effectiveness of infection control interventions depend highly on certain characteristics of the hospital, such as the proportion of susceptible patients, number of healthcare workers, and testing practices [20]. Effectiveness of individual interventions can also be affected by any other interventions used simultaneously, and the impact of multiple interventions is not likely additive. The effectiveness and cost of interventions can also be affected by the number of colonized or infected patients at any time. Currently, there is no tool to help infection control programs customize infection control intervention policies for their unique settings and requirements.

This chapter describes the formulation and numerical solutions of an optimal control model selecting infection control interventions over a finite time horizon subject to budget constraints. Our optimal control model derives parameters for each infection control intervention from an agent based model of hospital associated CDI. Because many hospitals can serve hundreds of patients, the "curse of dimensionality" quickly becomes a barrier to using a stochastic dynamic programming approach such as a Markov Decision Process [139]; thus, approximations are required. Optimal control modeling allows us to consider the aggregate transitions between different disease states in the hospital and assume a 'fluid' type transition model. As the outcomes of interest for hospital infection control purposes are aggregated at least by month, the stochasticity of daily events is less influential. Additionally, we assume that disease state transitions occur sufficiently often that the long term transition rates approach their averages by the law of large numbers. The optimal control approach also mirrors the well-accepted susceptible-infectious-recovered (SIR) approach for modeling infectious diseases, further strengthening the case for this type of model. In this chapter we present a novel approach to solving optimal control models using mixed integer programming. This framework provides an alternate for solving highly complex sequential decision making problem where the outcomes of actions are dependent on both the action itself and the system state.

5.1.1 Optimal control literature review

Optimal control models have been extensively used to characterize policies for controlling a dynamic system. These models have been used broadly in physics, engineering, and economics, with recent applications in the urban planning [140], energy [141], and automotive [142] industries, among many others. These models have also been used very widely in the fields of epidemiology and infectious disease control, with recent studies focusing on malaria [143, 144], tuberculosis [145], and COVID-19 [146, 147].

Optimal control studies often present the model formulation process, including the derivation of state constraints, the functional to be maximized/minimized, and any other relevant constraints. In the operations research literature, optimal control theory is commonly used to analyze fluid approximations of service systems [148–150]. These service system applications lend themselves well to more rigorous analysis, as these are often naturally linear in the control variable and shadow prices associated with each state variable have intuitive bounds. However, such structures are not common in the context of infectious disease, and as a result these models are solved primarily with numerical approaches. Some studies, like Lefévre's, reformulate their optimal control model as a

Markov Decision Process (MDP) that must be solved with typical MDP solution methods [151]. Blount, et al solve their optimal control model of a generic susceptible-infected-susceptible epidemic with a single control as a nonlinear program and again as a dynamic program [152]. Chehrazi, et al's work on the optimal antibiotic use policy for drug-resistant infections is an exception, as they provide a thorough structural analysis [153]. However, their particular model is more amenable to direct analysis, given that their state constraint differential equation is separable with respect to the control variable.

To our knowledge, there is very little literature examining the optimal control of CDI in hospitals. One of the few studies of this type was published by Stephenson, et al [154]. Their model characterized the dynamic optimal vaccination rate for CDI patients, in anticipation of CDI vaccines currently in trial. Stephenson, et al's model used seven major disease states: resistant, susceptible, colonized with protection against CDI, colonized without protection against CDI, vaccinated, colonized with vaccination, and infected. Their model also assumed an effectively closed population by allowing discharge and admission rates to balance out as a model constraint. Parameters were drawn from hospital data or published literature. Stephenson, et al used the Maximum Principal to analytically characterize the shadow prices associated with each disease state. Our model greatly differs from that of Stephenson, et al in several notable ways. First, our model uses multiple infection controls and makes strong consideration of the synergy between multiple infection control interventions. Second, our model does not attempt to parameterize the infection rate/exposure rate of CDI. Our model is one of the few models of disease transmission and control that avoids direct parameterization and relies on highly complex simulation to inform decision making. Third, the control of interest in Stephenson et al is independent of the system state. This is in contrast to our modeling approach, where the effectiveness of each intervention is dependent on the number of diseased or susceptible patients. Finally, Stephenson et al do not consider a budget constraint on the number of vaccines available to the hospital, and seek to jointly minimize vaccination-associated costs and CDIs. More studies focusing on other hospital-associated infectious diseases use a similar approach to Stephenson, et al [155, 156]. Zaric and Brandeau use heuristic methods to approximate the solution of an optimal control model with two interventions and parameterized, state-independent, non-linear intervention effectiveness functions (referred to as 'production functions') [157]. To the best of our knowledge, no optimal control model of a hospital-associated infection has been solved using primarily numerical methods or using parameters estimated via agent-based simulation.

5.2 Optimal Control Model Formulation

5.2.1 Generic infection

Our optimal control model represents the change in patient disease distribution within a single hospital for some generic infectious disease. Disease distribution is controlled through bundles of infection control interventions that may be altered over the time horizon. We assume a finite, continuous time horizon $[0, T]$, representing a single budget planning period such as one year. We assume that an infection control professional may select from a finite set N of infection control interventions to create infections control bundles and policy. Resources may be allocated to each intervention in N to achieve varying levels of compliance and effectiveness. We let $u_n(t) \in [0, \bar{u}_n]$ represent the amount of spending on intervention $n \in N$ at time t and $u(t) = (u_1(t), ..., u_{|N|}(t))$.

We assume that each intervention in N has some upper limit on spending $\bar{u}_n$.

We let K represent the finite set of disease states patients may occupy in the model, and assume that all patients in the hospital occupy some state $k \in K$. The elements of K will vary depending on the infectious disease, but we assume K will always contain some state that represents diseased patients: for the remainder of this section we will refer to such state as 'infected.' We also assume that the set K will contain a 'colonized' or 'latent' state, where the pathogen incubates before potentially causing an infection (though a patient may be infectious during this period). This is common in the context of hospital-associated infectious diseases and infectious diseases broadly. We represent the number of patients in the hospital of disease type $k \in K$ at time $t \in [0, T]$ as $x_k(t)$. We also include an additional state variable $b(t)$ representing the amount of resources available for infection control interventions at some time t.

Hospitals generally have a fixed number of beds, and therefore can serve a finite number of patients at any given time. However, hospitals generally operate at some steady state capacity where the rate of new arrivals is balanced by the rate of discharge. This balance is not normally violated in the context of hospital-associated infections, as hospitals are highly unlikely to be inundated by infected patients and surpass their normal steady state operating capacity. Therefore, we may assume that the number of patients in the hospital at any given time is bounded above,

$$\mathbf{1}_{|K|} x(t) \leq H, \quad t \in [0, T], \tag{5.1}$$

where $\mathbf{1}_{|K|}$ is a vector of ones of length $|K|$. Similarly, we denote the total budget over

$[0,T]$ as b^0 and model the relationship change in $b(t)$ subject to controls $u(t)$ as

$$\dot{b}(t) = -\mathbf{1}_{|N|}u(t), \quad t \in [0,T], \tag{5.2}$$

$$b(0) = b^0, \tag{5.3}$$

$$b(T) \geq 0. \tag{5.4}$$

We note that 5.4 simply requires that we cannot spend more than b^0 over the time horizon (as we can only deplete resources over the time horizon). This relationship mirrors the fixed budget constraint over a finite time horizon as expressed in Sethi's analysis of a constrained optimal control model [158].

Patients arrive at the hospital at time t with a rate of l and may be discharged from the hospital at some rate $\beta(x,u) = [\beta_1(x,u), ..., \beta_{|K|}(x,u)]$. We let $d(x,u) = [d_1(x,u), ..., d_{|K|}(x,u)]$ be the average death rate at time t. We may also allow the vector $\alpha \in \mathbb{R}^{|K|}_{\geq 0}$ to represent the proportion of newly arrived patients in disease state $k \in K$. Let $G(u,x) \in \mathbb{R}^{|K|\times|K|}$ represent a matrix of transition rates between disease states in K. Notably, d, β, G are functions of the state and control, and are the primary means by which the control u affects the system. The exact functions defining these relationships will vary with each infection and its common infection controls and treatments. For instance, diseased patients in a hospital with high infection prevalence may be more likely to die if treatment resources are normally scarce, regardless of infection controls.

At $t = 0$, we denote the initial disease distribution as x^0. We additionally require that the number of patients in each disease state must be non-negative (i,.e., $x(t) \geq 0$). We may represent the rate of change in the number of patients in the hospital in disease state k at time $t \in [0, T]$ as

$$\dot{x}(t) = \alpha l(t) - d(x,u)x(t) - \beta(x,u)x(t) + x(t)G(u,x), \quad t \in [0,T], \tag{5.5}$$

$$x(t) \geq 0, \tag{5.6}$$

$$x(0) = x^0. \tag{5.7}$$

We assume that the goal of the decision maker is to minimize the total infectious disease-related cost in the hospital. If $c \in \mathbb{R}^{|K|}_{\geq 0}$ represents some cost vector, then the full optimal control model can be written as

$$\begin{aligned} \text{maximize}_u \quad & \int_0^T -cx(t)dt \\ \text{subject to} \quad & (5.1) - (5.7). \end{aligned} \tag{5.8}$$

5.2.2 CDI optimal control model

Hospitals are immensely complex systems, and several simplifying assumptions are essential to create a practical model. The first of these assumptions is to limit the model focus to only on CDI patients. The model will not explicitly consider the impact of other diseases on the progression or risk of CDI.

To adapt the optimal control model 5.8 for hospital-associated CDI, we apply multiple disease specific assumptions. We use the discrete time Markov Chain described in our ABM publications and shown in Figure 5 as a starting point [20, 63, 94]. We know that the population of ‘recolonized’ and ‘recurrent infected’ patients is typically very small and can be estimated as a proportion of the number of infected patients. We may also eliminate the ‘exposed’ and ‘cleared’ states, as patients spend a very short amount of time in these states before immediately transferring (with probability 1) to a different disease state. Therefore, we can eliminate these states from consideration and the set K of CDI disease states for inclusion in the optimal control model is

$$K = \{\text{colonized (C), infected (I), susceptible (S), non-susceptible (N)}\}.$$

In the context of *C. difficile*, most flow rates between infection states are unaffected by the infection controls in place or the state of the hospital. Therefore, we can decouple the state/control dependent and independent flow rates into two separate structures. Moving forward, we represent the former as $G(u, x)$, and the latter as $\mathcal{P} \in \mathbb{R}_{[0,1]}^{|K|\times|K|}$. We will refer to $G(u, x)$ as the 'exposure rate' because this value characterizes the rate at which susceptible patients are exposed to *C. difficile*, whether by interaction with the environment or another person. We would expect for the exposure rate to increase under poor infection control, or when the prevalence of CDI is high. We let $q \in [0, 1]^{|K|}$ represent the proportion of exposures immediately transitioning into each infection state. In the context of CDI, $d(x, u)$ and $\beta(x, u)$ can be reduced to constant rates d, and β, respectively. This assumption is valid for hospital-associated CDI in particular. CDI is a common and well known infection, and does not require (relatively) extensive resources for treatment. Therefore, hospitals do not have to 'ration' treatment among CDI patients, and a higher population of infected patients should not compromise an individual patient's access to CDI treatments. This contrasts with diseases like Covid-19, for which treatment resources like ventilators are generally scarce and large influxes of infected patients theoretically have detrimental impacts on individual patient outcomes.

The state constraint for the CDI optimal control model can then be expressed as,

$$\dot{x}(t) = \alpha l - dx(t) - \beta x(t) + x(t)\mathcal{P} + qG(u, x). \tag{5.9}$$

and the full CDI optimal control model J_{CDI} as,

$$\begin{aligned} \text{maximize}_u \quad & \int_0^T \{-cx(t)\}dt \qquad (J_{CDI}) \\ \text{subject to} \quad & (5.1)-(5.4),(5.6)-(5.7),(5.9). \end{aligned}$$

We provide a discussion of conditions which would be conducive to a monotonic policy for a simplified, single-control version of J_{CDI} in Appendix A.4.1.

5.3 MIP reformulation

Like many optimal control models with multiple state variables, J_{CDI} is highly intractable and cannot be solved analytically. Additionally, many of the relationships in the optimal control model, such as the exposure rate G, are likely nonlinear in x, u and therefore difficult to characterize with confidence. To eliminate the need to characterize these functions, we reformulate J_{CDI} as a mixed integer program (MIP) by discretizing the state and action variables, and by extensively leveraging our ABMs.

We use $\tau = \{0, 1, ...T\}$ to designate the finite, discrete time horizon. To discretize our state space for the optimal control MIP, we adopt a grid-based approach and generate a set of values in $\mathbb{R}^{|K|}_{\geq 0}$, representing several possible infection state distributions in the hospital. We denote the full set of grid state distribution points as W. Then, any feasible distribution of disease states in the hospital may be represented as a convex combination of elements in W. Similarly, we assume that each of the infection control interventions in the set N may be set to one of h known levels of effectiveness/performance and cost. We let V be the set of possible infection control bundles made of the N controls. Then, $|V| = h^{|N|}$. We note a subtle shift in the discretized model concerning the control variables. For the discretized model, the control instead becomes a binary variable $u_v^t, t = 1, ..., T$, associated with each possible infection control bundle $v \in V$. This differs from J_{CDI}, where the decision maker instead controls the amount spent at any given time.

For each element (v, w) in the grid $V \times W$ we associate a per time step value of $G(v, w)$ and $r(v, w)$, where $r(v, w)$ is the cost associated with implementing intervention bundle v starting in hospital state w. We introduce the variable δ_w^t, representing the convex combination multiplier for grid element $w \in W$ at time t and γ_{vw}^t as an additional multiplier for each $(v, w) \in V \times W$. Then, we may use the grids V, W to a write any feasible x^t, G^t as a convex combination of grid elements, i.e.,

$$x^t = \sum_{w \in W} \delta_w^t w, \quad t = 0, 1, ..., T \tag{5.10}$$

$$1 = \sum_{w \in W} \delta_w^t, \quad t = 0, 1, ..., T \tag{5.11}$$

$$\delta_w^t \in [0, 1], \forall w \in W \quad t = 0, 1, ..., T \tag{5.12}$$

and

$$G^t(u, x) = \sum_{v \in V} \sum_{w \in W} \gamma_{vw}^t G(v, w), \quad t = 0, 1, ..., T \tag{5.13}$$

$$\sum_{v \in V} u_v^t = 1, \quad t = 0, 1, ..., T \tag{5.14}$$

$$\gamma_{vw}^t \leq u_v^t, \quad \forall (v, w) \in V \times W, t = 0, 1, ..., T \tag{5.15}$$

$$\gamma_{vw}^t \leq \delta_w^t, \quad \forall (v, w) \in V \times W, t = 0, 1, ..., T \tag{5.16}$$

$$\gamma_{vw}^t \geq \delta_w^t - (1 - u_v^t) \quad \forall (v, w) \in V \times W, t = 0, 1, ..., T \tag{5.17}$$

$$u^t \in \{0, 1\}^{|V|}, \quad t = 0, 1, ..., T. \tag{5.18}$$

In Appendix A.4.2 we briefly present a pair of constraints that enforce the same relationship as 5.15, 5.16, and 5.17 while producing a more concise formulation. All the results presented in this chapter use the formulation including constraints 5.15, 5.16, and 5.17. We may use the same γ variables to also define the cost for each intervention bundle for each time step. Similarly to the exposure rate, the cost $r^t(u,x)$ of some infection control bundle employed at time t can be expressed as

$$r^t(u,x) = \sum_{v \in V} \sum_{w \in W} \gamma^t_{vw} r(v,w), \quad t = 0, 1, ..., T. \tag{5.19}$$

The budget constraint may be expressed as,

$$\sum_{t=\tau} r^t(u,x) \le b^0. \tag{5.20}$$

In a realistic hospital setting, infection control professionals cannot select control bundles every time step (assuming the time step is small), as the requirements to reallocate resources often would quickly exceed financial and human resource capabilities. Hospitals must select a decision-making schedule, or 'scheme', to change infection control policy. To model decision-making schemes, we use the parameter ζ to represent the number of discrete time steps between decisions. For example, if each $t \in \tau$ represents one day and a decision maker uses a weekly decision-making scheme, then $\zeta = 7$. This necessitates constraints for every $\bar{t} \in \{t \in \tau | t \bmod \zeta = 0\}$ of the form,

$$u^{\bar{t}} = u^{\bar{t}+1} = ... = u^{min(\bar{t}+\zeta-1,T)}. \tag{5.21}$$

We note that the grid required for this formulation increase in size quickly as the number of grid points in W increases. One assumption we can make to ensure that W is not excessively big or exhibits a large reduction in estimate quality at extremal points is to assume that the modeled hospital is always operating at some capacity $\bar{H} < H$.

We believe this assumption is reasonable, as hospitals typically operate at some steady proportion of their total capacity: typically between 60-80% [159, 160]. Other optimal control models of hospital-associated infection have also assumed a fixed hospital population size [154, 155]. From a modeling standpoint, this allows us to use smaller cost and exposure rate grids to reduce computational load. This translates to the constraint

$$\sum_{k \in K} \sum_{w \in W} \delta_w^t w_k = \bar{H}, \quad t = 0, 1, ..., T+1. \tag{5.22}$$

We allow the arrival rate l^t to be set by the model in order to maintain hospital capacity $\bar{H}$. To fit the MIP formulation, we can approximate $x(t)$ using a first-order, Euler approximation where $x(t+1) = \dot{x}(t)dt + x(t)$. Using this approximation and $P \in \mathbb{R}^{|K| \times |K|}$, a transition probability matrix for states in K modified from the matrix depicted in Figure 5, we may re-write our x state constraints for each $t = 0, 1, ..., T$ as

$$\sum_{w \in W} \delta_w^{t+1} w = \alpha l^t - d \sum_{w \in W} \delta_w^t w - \beta \sum_{w \in W} \delta_w^t w + [\sum_{w \in W} \delta_w^t w] P + q \sum_{v \in V} \sum_{w \in W} \gamma_{vw}^t G(v, w). \tag{5.23}$$

Combining the preceding constraints, the final discretized MIP M' is:

$$\begin{aligned} \text{maximize}_{u,l} \quad & -[\sum_{w \in W} \delta_w^t w]_C - [\sum_{w \in W} \delta_w^t w]_I \\ \text{subject to} \quad & (5.10) - (5.23). \end{aligned} \tag{M}$$

The MIP M minimizes the total number of colonized and infected patient days. In Appendix A.4.3 we discuss an alternate objective function with the goal of minimizing an estimate of the total number of HA-CDIs. The results in this chapter are all obtained using variants of M.

5.3.1 Policy variants

In most hospitals, infection control policy is often set at the beginning of the planning period and carried out unchanged throughout the planning period duration. Typically, adjustments could be made in the event of outbreaks or an influx of additional resources. Therefore, highly dynamic policies are not practical in a hospital infection control decision making context and we must make a few crucial simplifying assumptions.

First, we assume that infection control decisions are made only at the beginning of each month (i.e., $\zeta = 30$). This is meant to reflect a reasonable resource decision making schedule for an infection control program. Second, we split the policies of interest into three types, as further described below.

- Fully dynamic (D): these policies are those for which the infection bundle in effect is allowed to change at every decision period (i.e. month). These policies would naturally represent the best case for infection control, as these policies allow for the most freedom to re-allocate resources in response to CDI rates. This MIP is represented by M.
- Control limit (CL): these policies follow a non-increasing pattern during the time horizon. These policies allow for interventions to be 'turned off' at some point during the planning horizon, after which they may not be 'turned on' again. This

MIP can be written as:

$$\text{maximize}_u \quad \sum_{t\in\tau} -[\sum_{w\in W} \delta_w^t w]_C - [\sum_{w\in W} \delta_w^t w]_I \tag{M_{CL}}$$

subject to $\quad (5.10) - (5.23)$

$$\sum_{v\in V} u_v^t Y_{vn} \geq \sum_{v\in V} u_v^{t+1} Y_{vn}, \quad \forall t = 0,1,...,T-1, \forall n \in N \tag{5.24}$$

Where,

$$Y_{vn} = \begin{cases} 1, \text{intervention } n \text{ is included in active bundle } v \text{ at time t} \\ \\ 0, \text{o.w.,} \end{cases} \tag{5.25}$$

and constraint 5.24 ensures that each infection control intervention in the set N is non increasing over the full planning period. We label instances of this MIP as M_{CL}. In Appendix A.4.4 we provide a generalization of this policy style that allows for interventions to be first turned 'on' later in the planning horizon.

- Static (S): these policies require that only a single infection control bundle is used over the entire planning horizon. These policies are the simplest, and do not allow for any change in policy over time. We note that costs and exposure rates will change under these policies, but the infection control decision remains static. This MIP can be written as:

$$\text{maximize}_u \quad \sum_{t\in\tau} -[\sum_{w\in W} \delta_w^t w]_C - [\sum_{w\in W} \delta_w^t w]_I \tag{M_S}$$

subject to $(5.10) - (5.23)$

$$u^t = \mathbf{u}, \quad \forall t = 0,1,...,T \tag{5.26}$$

Where 5.26 is an additional constraint that sets all the dynamic u^t equal to some static bundle $\mathbf{u}$ that is selected by the MIP. We label instances of this MIP as M_S.

As shown in previous studies, solving an optimal control model often admits a solution that is highly dynamic and impossible to implement in real life scenarios [152]. Therefore, we are primarily interested in contrasting these three types of policies in order to quantify the 'cost' of implementability in infection control. We are also interested in assessing how the cost of implementability changes under different hospital conditions, and under what circumstances (if any), does a simpler policy dominate more dynamic options. We strongly believe that the primary managerial insights of this study are not in the policies themselves, but the relationships between hospital conditions, policies, and relative utilization of each infection control intervention.

5.4 Numerical Results

To analyze the effects of hospital-specific characteristics on infection control policy, we use two different ABMs to estimate G, r. Specifically, we use both the generic community hospital model described in previous publications [20, 63], and the academic hospital model described in Chapter 4.

To develop infection control bundles, we considered four interventions: hand hygiene, environmental cleaning, screening at admission/surveillance, and contact precautions. Each of the four broad interventions represents a bundle of at least one other intervention for which the CDI ABMs contain logic for. For example, 'hand hygiene' refers to the bundling of patient, doctor, nurse and visitor hand hygiene interventions. We also considered two levels for each intervention ($h = 2$); a 'baseline' level with minimal investment from the hospital, and a 'fully implemented' level with full administrative and systemic backing. We considered these 'on-off' style interventions for two reasons:

first, it is not always practical for infection control professionals to 'partially' implement different infection control interventions, especially those that would require workforce behavioral changes. Second, this discrete 'on-off' format was essential to maintaining MIP structural requirements.

For the community hospital results we used a W grid of 33 elements (29 intermediate states, 4 extreme states, one empty hospital state). For the academic hospital model, we used 35 intermediate states, along with the 4 extreme states and the empty hospital state. Exposure rate and costs were obtained for each element in the grid $V \times W$. Exposure rates for each element in $V \times W$ were calculated using counts of the number of exposures in the agent-based simulation. Bundle cost estimates were derived from the agent based simulation using estimates for the cost of each intervention-related event. The total cost of each intervention bundle was calculated using the counts of infection control events in the simulation multiplied by the unit cost of the event. Costs may be altered to include the labor cost of certain interventions. If labor costs are applicable and included, the agent's average hourly wage and duration of each infection control event is used to calculate the total labor cost. For example, to calculate the cost of nurse hand hygiene over the simulation period, we collected a count of the number of times a nurse agent performed a hand hygiene event. This number was multiplied by the cost of hand hygiene materials and by the nurse's average hourly wage and the duration of a hand hygiene event (in hours). All bundle cost estimates were converted to a cost per time step. Estimates for material costs, as well as estimates of average hourly wages and event duration were drawn from our group's previously published cost-effectiveness study of CDI infection control interventions [161]. We note that the exposure rate and cost grids had to be recalculated for each experiment case as changes in hospital conditions (e.g., case where all hospital patients are susceptible to CDI), can greatly change the model dynamics influencing these estimates.

The estimation of the number of hospital-associated infections from the MIP is not a reliable metric to express the true effectiveness of each optimal policy. Therefore, for each policy obtained with the MIP, we ran the policy using the corresponding ABM to obtain more reliable estimates of the resultant HA-CDIs/per 10k patient days. This value as estimated from 500 simulation replications is the rate of HA-CDI we report for each experimental case.

We also note that, as a result of the limitations of a MIP and grid-based framework, it is possible that the policies obtained by M and its variants are not 'truly' optimal. We certainly acknowledge this is true, but we note that even the likely sub-optimal policies presented in this study represent an improvement in baseline infection control practices. We also note that as long as our V, W grids remain internally consistent with respect to u, we are comfortable comparing policies across different hospital characteristics.

We solve the MIP for a range under various hospital conditions, described in detail below:

- Baseline: we first consider the 'baseline' case for the community hospital. This case uses the baseline ABM parameters describing both infection control interventions and common hospital characteristics.

- Double colonized, infected: we consider a case where the proportion of colonized and infected patients at admission are doubled. This could arise in the case of an outbreak of CDI in the community or in another healthcare facility (such as a long term care facility or skilled nursing facility).

- All susceptible: we consider the cases where all patients arriving at the hospital are susceptible to CDI (with the exception of those who arrive colonized or infected with *C. difficile*). This could represent a hospital in communities with a high proportion of older adults, or a Veterans' Hospital.

- Half baseline: we consider a case where the parameters associated with each infection control intervention (i.e., the 'off' parameters) are half their baseline levels. This case is meant to illustrate how optimal infection control policies change depending on the level of infection control a hospital is able to maintain at baseline. This case could be salient to hospitals that struggle with maintaining infection control practices without significant investment.

- Academic hospital: these experiments use the H-ABM described in Chapter 4 to estimate our costs and exposure rate grids. We also use different parameters relating to capacity, arrival rate, and susceptibility to fit the profile of a larger hospital.

We believe these varied conditions capture several of the common hospital operating conditions in the United States. We hope that by testing each of these cases, we will be able to obtain results that can hold managerial insight to infection control professionals working in a variety of environments.

Table 9 displays the estimates and sources for various baseline parameters used in both the community and academic hospital MIPs. Tables 10 and 11 contain parameters specific to the community and academic hospital models, respectively.

Table 9: Common MIP parameters, for both community and academic models

Description	**Value**	**Source**
Death rate: infected patients	0.0015	[94]
Death rate: susceptible, non-susceptible, and colonized patients	0	[94]
Exposures, immediately transitioning to susceptible	0.6311	[94]
Exposures, immediately transitioning to colonized	0.2964	[94]
Exposures, immediately transitioning to infected	0.0725	[94]
Proportion colonized at admission	0.0606	[20]
Proportion infected at admission	0.0029	[20]
Antibiotic prescription rate	0.1	[20]

Table 10: Community hospital model MIP parameters

Description	**Value**	**Source**
Hospital capacity	125	[20]
Arrival rate	26	[20]
Proportion susceptible at admission (baseline)	0.3967	[20]
Proportion non-susceptible at admission (baseline)	0.4763	[20]

Table 11: Academic hospital model, MIP parameters

Description	**Value**	**Source**
Hospital capacity	307	ABM
Arrival rate	70	HD
Proportion susceptible at admission (baseline)	0.4974	HD
Proportion non-susceptible at admission (baseline)	0.4391	HD

HD = Hospital data

Each $t \in \tau$ represents a single day. In all experiments we assume that the planning period is 12 months and infection control decisions may be made only at the start of each month ($\zeta = 30$). The MIP model was written with Julia's JuMP package and solved using the Gurobi solver (academic license). All experiments were run on a single desktop computer with an Intel Core i5-8500 CPU and 16GB RAM. As each MIP proved highly difficult to solve, we conserved computational effort as much as possible by 'warm-starting' each MIP with a feasible solution when possible. For example, we would warm-start the M MIP with the optimal solution from M_{CL}, thereby reducing the computational requirement of M while ensuring that M will outperform M_{CL} as expected. We solve each M_{CL}, M_S to a MIP gap of at most 1%. However, even with a warm-start, we were often only able to obtain a MIP of approximately 5% for M.

5.4.1 Community Hospital Model

Baseline

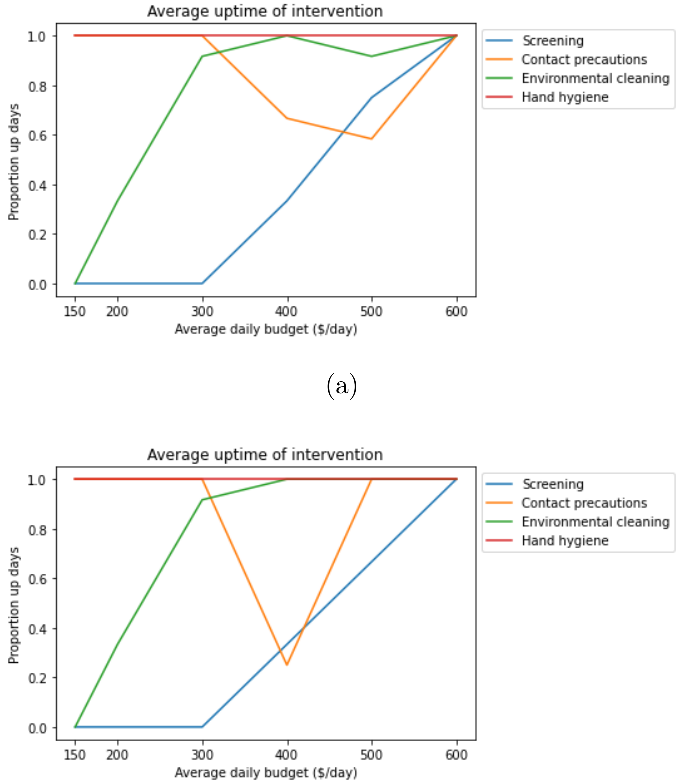
Figure 8 depicts the average infection control policy for the community hospital over 12 months, subject to varying budgets constraints. This figure plots the individual status of each of the four different infection controls over the full planning period. To provide a qualitative understanding of how ‘much’ each infection control intervention is used, Figure 9 plots the proportion of ‘uptime’ (i.e., the proportion of days for which a specific intervention is in use) for each of the four infection control interventions. We observe that the uptime for each intervention does not appear to differ dramatically between the control limit and dynamic policies. Additionally, the screening uptime appears to be non-decreasing as the average daily budget increases. This is in contrast to the uptime for contact precautions, which exhibits a sustained period of lower use in the middle-high budget range. This period of downtime notably starts when it becomes optimal to include screening at admission in the optimal infection control policy.

(a)

(b)

(c)

Figure 8: Optimal infection control policy, dynamic (a), control limit (b), and static (c)



(a)

(b)

Figure 9: Optimal infection control policy uptime by budget for baseline community hospital, dynamic (a) and control limit (b)

Table 12 displays the simulated rates of HA-CDI per 10,000 patient days and total costs for each type of policy under various budgets. In most cases, the performance gap between the dynamic and control limit (D/CL) policies is small ($< 1\%$), while the control limit and static (CL/S) policy gap is relatively large. Additionally, for each budget band, the total amount spent on infection control interventions (as provided in the 'Total Costs' column) are generally non-decreasing as the resultant rate of HA-CDI decreases. These results are visualized in Figure 10.

Table 12: HA-CDI rate and total cost by policy and budget for baseline community hospital

Average daily budget ($)	HA-CDI/10000 Patient Days					Total Costs ($)		
	Dynamic	Control Limit	Static	D/CL Gap	CL/S Gap	Dynamic	Control Limit	Static
600	1.06	1.06	1.06	0.0%	0.0%	185818	185818	185818
500	1.16	1.17	1.37	0.9%	14.6%	158226	156029	142674
400	1.33	1.34	1.48	0.7%	9.3%	124427	125550	94862
300	1.60	1.60	2.23	0.0%	28.3%	91154	91154	78952
200	2.50	2.61	3.19	4.5%	18.0%	65916	65848	51550
150	3.19	3.19	3.19	0.0%	0.0%	51550	51550	51550

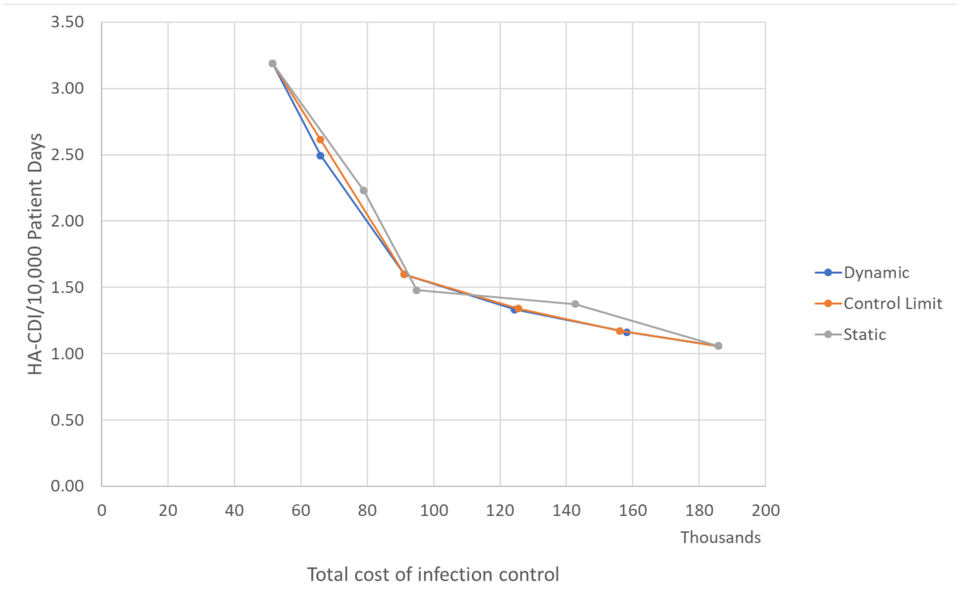


Figure 10: Simulation estimation of HA-CDI vs total cost, community hospital model

Table 13 displays the incremental cost-effectiveness ratios (ICERs) associated with switching from the corresponding optimal static policy at each budget to the policies listed in the left-hand column. We omit the ICERs for any budgets where all three policy types were identical. For this brief cost-effectiveness analysis, we only consider the costs associated with the infection control intervention policy and the costs of each HA-CDI: we do not discount any costs or health outcomes. We calculate the ICERs for three HA-CDI costs, with $12000 roughly representing the national average [161]. It is clear that the cost-effectiveness of switching from a static policy to a control limit or dynamic policy depends greatly on the estimated cost of an infection in a specific hospital, which can vary greatly by region. Additionally, for the baseline case, it is generally not cost-effective to switch from a static to dynamic/control limit policy when the infection control budget is generous (given a willingness to pay up to the cost of an individual infection). This is a reasonable finding, as we would expect infection control programs operating under tighter budgets to benefit disproportionately from dynamic resource allocation policies.

Table 13: Cost-effectiveness analysis, Base case, community hospital

Policy	ICER (Reference: S)		
	Cost of infection = \$12,000	Cost of infection = \$24,000	Cost of infection = \$9,000
\$500, D	-61374	-49374	-64374
\$500, CL	-54502	-42502	-57502
\$400, D	-188909	-176909	-191909
\$400, CL	-210752	-198752	-213752
\$300, D	-7312	4688	-10312
\$300, CL	-7312	4688	-10312
\$200, D	-8788	3212	-11788
\$200, CL	-12951	-951	-15951

Baseline, 5 year time horizon

The relatively strong performance of control limit policies, which allow interventions to relax after specific times in the planning period, may be surprising. Additionally, it would be reasonable to question the performance of such policies when implemented over more than a single planning period. To test the performance of our three policy types over a longer time horizon, we simulate an optimal policy that repeats over five continuous years. The optimal policy tested in each case is the same as those visualized in Figure 8. As displayed in Table 14, the performance of dynamic and control limit policies over five years is comparable to the performance over a single year.

Table 14: HA-CDI rate and total cost by policy and budget for baseline community hospital over 5 years

Average daily budget ($)	HA-CDI/10000 Patient Days					Total Costs ($)		
	Dynamic	Control Limit	Static	D/CL Gap	CL/S Gap	Dynamic	Control Limit	Static
600	1.07	1.07	1.07	0.00%	0.00%	923888	923888	923888
500	1.23	1.22	1.38	-0.89%	11.65%	785074	774378	708365
400	1.33	1.34	1.48	0.52%	9.58%	621725	622282	473896
300	1.60	1.60	2.27	0.00%	29.64%	455705	455705	394394
200	2.51	2.61	3.22	3.77%	19.14%	329496	329368	257625
150	3.22	3.22	3.22	0.00%	0.00%	257625	257625	257625

Double infected and colonized at admission

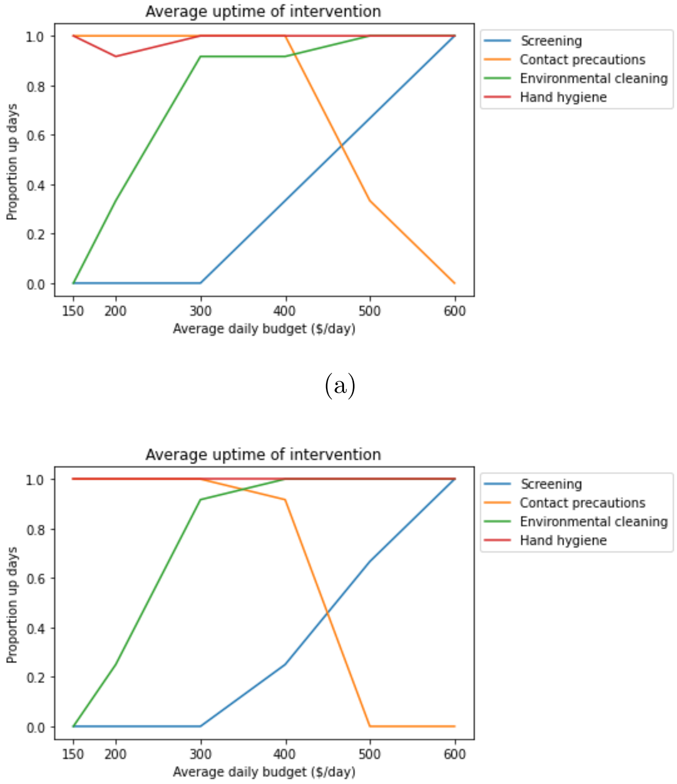
To explore the impact of a higher infected/colonized population, we solve the MIPs for the community hospital model where the proportion of patients colonized or infected with *C. difficile* at admission is doubled. Figure 11 depicts the infection control policy for the community hospital over 12 months, subject to varying budget constraints. Table 15 records the performance and cost of each policy. Notably, with the exception of the relatively tight budget averaging $200 per day, the CL/S gaps are larger for the higher colonized and infected population compared to the baseline case. Figure 12 plots the uptime proportion for each of the four infection control interventions. The uptime for environmental cleaning and screening at admission are similar to those in the baseline case (Figure 9), but the region of lower contact precaution use is shifted to a higher average daily budget range. Likely, this is because environmental cleaning and screening become more expensive with higher prevalence of colonized and infected patients, and any portion of the budget that could be spent on contact precautions must be spent to maintain these high-impact interventions. Table 16 displays the ICERs associated with shifting away from the static policy at each budget level. Notably, shifting from the static policy to the dynamic of control limit policy is more cost-effective in this higher infected/colonized prevalence than in the baseline case, for each budget band. Also, as in the baseline cases, shifting to a dynamic/control limit policy is generally more cost-effective for tighter budgets.

(c)

Figure 11: Optimal infection control policy with double colonized/infected, dynamic (a), control limit (b), and static (c)

Table 15: HA-CDI rate and total cost by policy and budget for community hospital with double colonized and infected patients

Average daily budget ($)	HA-CDI/10000 Patient Days					Total Costs ($)		
	Dynamic	Control Limit	Static	D/CL Gap	CL/S Gap	Dynamic	Control Limit	Static
600	1.09	1.09	1.09	0.0%	0.0%	196115	196115	196115
500	1.33	1.33	1.56	-0.4%	15.3%	157644	158520	153295
400	1.63	1.65	1.84	1.5%	10.3%	125294	121885	95699
300	2.04	2.04	3.28	0.0%	37.9%	91999	91999	79845
200	3.48	3.66	4.30	4.8%	14.9%	65547	63247	52529
150	4.30	4.30	4.30	0.0%	0.0%	52529	52529	52529



(a)

(b)

Figure 12: Optimal infection control policy uptime by budget for community hospital with double the infected and colonized patients, dynamic (a) and control limit (b)

Table 16: Cost-effectiveness analysis, double infected and colonized, community hospital

Policy	ICER (Reference: S)		
	Cost of infection = $12,000	Cost of infection = $24,000	Cost of infection = $9,000
$500, D	-6580	5420	-9580
$500, CL	-9859	2141	-12859
$400, D	-126196	-114196	-129196
$400, CL	-125909	-113909	-128909
$300, D	2213	14213	-787
$300, CL	2213	14213	-787
$200, D	-3918	8082	-6918
$200, CL	-4705	7295	-7705

All susceptible

We run the MIPs for cases where all patients entering the community hospital are susceptible at admission (with the exception of already colonized or infected patients). The policy visualization is provided in Figure 13. Table 17 summarizes the HA-CDI rate and costs associated with the optimal policies in this case. As seen in the uptime plots (Figure 14), environmental cleaning and screening at admission are again generally increasing as the average daily budget increases. Finally, shifting to a dynamic/control limit policy is overall more cost-effective with a high susceptible population than compared to the baseline case (Table 18).

(a)

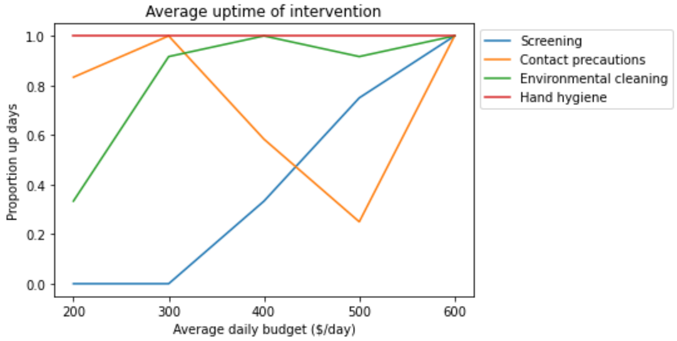
(b)

(c)

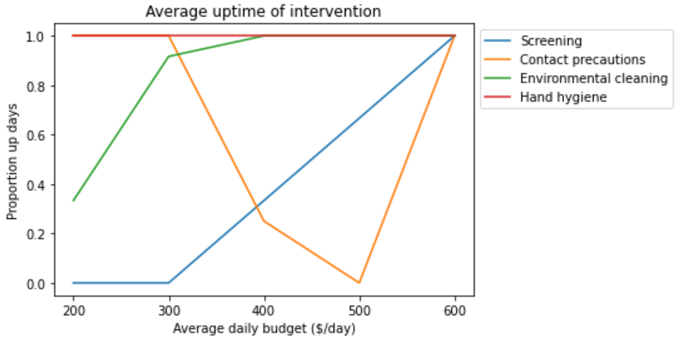
Figure 13: Optimal infection control policy for hospital with all patients susceptible, dynamic (a), control limit (b), and static (c)

Table 17: HA-CDI rate and total cost by policy and budget, all patients susceptible

Average daily budget ($)	HA-CDI/10000 Patient Days					Total Costs ($)		
	Dynamic	Control Limit	Static	D/CL Gap	CL/S Gap	Dynamic	Control Limit	Static
600	2.00	2.00	2.00	0.0%	0.0%	185964	185964	185964
500	2.23	2.24	2.78	0.4%	19.4%	157054	153212	142929
400	2.47	2.47	2.71	-0.3%	8.9%	123645	125733	95130
300	2.93	2.93	4.48	-0.1%	34.6%	91444	91444	79405
200	4.88	5.14	6.45	5.0%	20.3%	66393	66451	52264



(a)



(b)

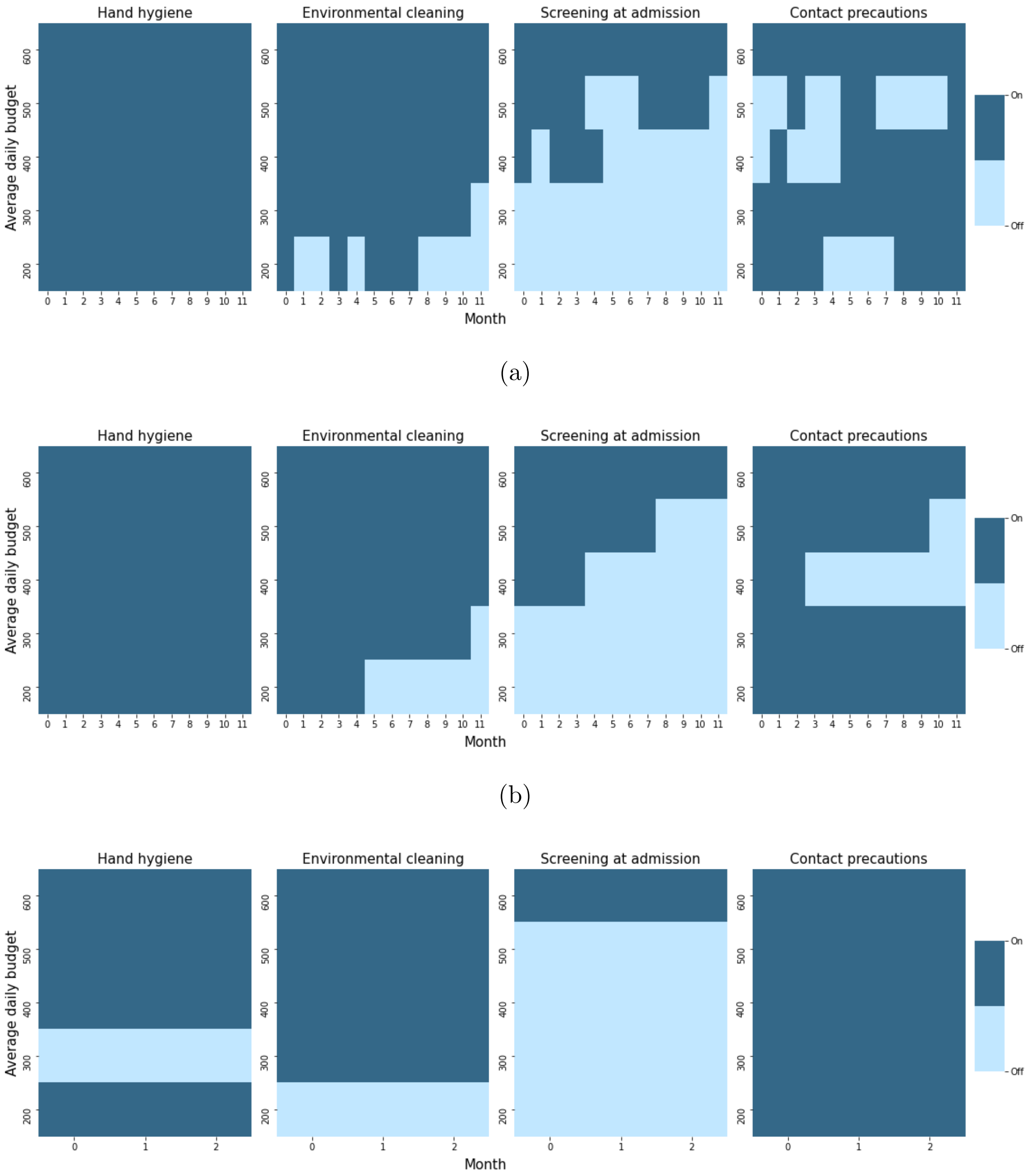
Figure 14: Optimal infection control policy uptime by budget for community hospital with all susceptible patients, dynamic (a) and control limit (b)

Table 18: Cost-effectiveness analysis, all patients susceptible, community hospital

Policy	ICER (Reference: S)		
	Cost of infection = \$12,000	Cost of infection = \$24,000	Cost of infection = \$9,000
\$500, D	-13681	-1681	-16681
\$500, CL	-7042	4958	-10042
\$400, D	-109215	-97215	-112215
\$400, CL	-114322	-102322	-117322
\$300, D	4211	16211	1211
\$300, CL	4233	16233	1233
\$200, D	2980	14980	-20
\$200, CL	1170	13170	-1830

Half baseline compliance

We recognize that the modeled baseline levels of each intervention could be overly optimistic for several community hospitals. To assess the impact of the baseline level of each interventions, we solve the MIPs for a community hospital where the compliance with each infection control intervention is half of that in the baseline case. Notably, the CL/S gaps included in Table 19 are larger than those in the other community hospital model cases. This is unsurprising, given the lower compliance and thus performance of the baseline interventions. Much like the other community hospital cases, we can see that the uptime of environmental cleaning and screening at admission increase as the average daily budget increases (Figure 16). The use of contact precautions appears to be complementary in this case as well.



(a)

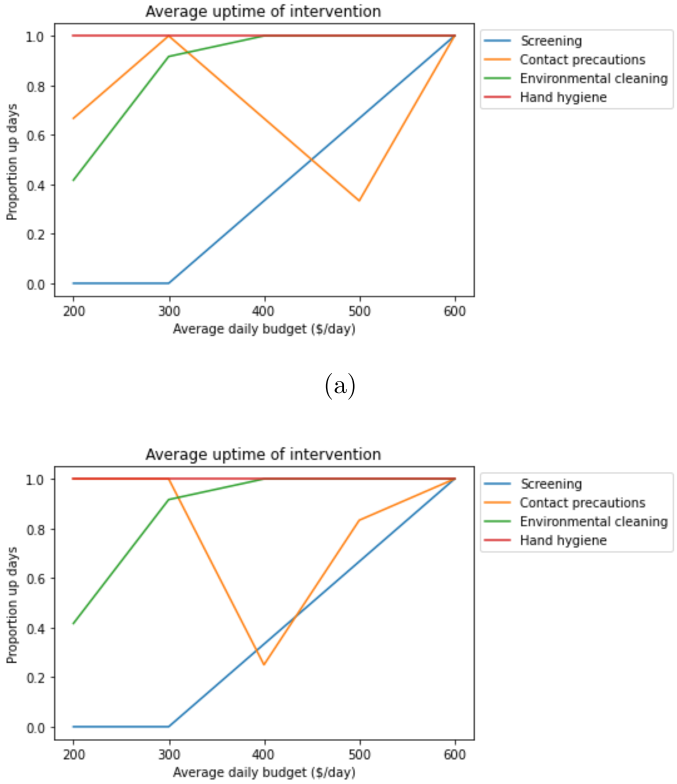
(b)

(c)

Figure 15: Optimal infection control policy for hospital with half baseline intervention compliance, dynamic (a), control limit (b), and static (c)

Table 19: HA-CDI rate and total cost by policy and budget, half intervention baseline compliance

Average daily budget ($)	HA-CDI/10000 Patient Days					Total Costs		
	Dynamic	Control Limit	Static	D/CL Gap	CL/S Gap	Dynamic	Control Limit	Static
600	1.07	1.07	1.07	0.0%	0.0%	185745	185745	185745
500	1.21	1.20	1.58	-0.9%	24.2%	151946	155934	94849
400	1.34	1.33	1.58	-0.4%	15.8%	123841	125194	94849
300	1.88	1.88	4.10	0.0%	54.2%	90480	90480	70054
200	3.85	4.17	6.31	7.8%	33.9%	65035	65179	44191



(a)

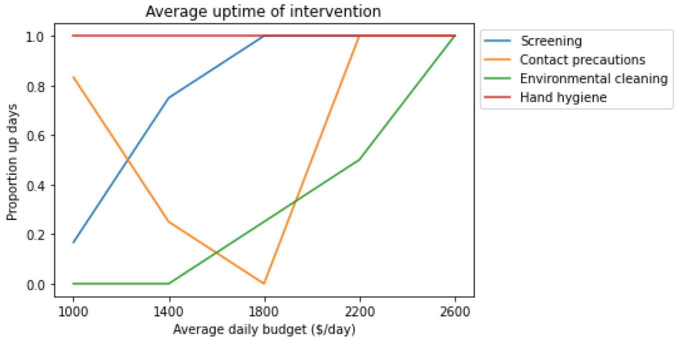
(b)

Figure 16: Optimal infection control policy uptime by budget for community hospital with half baseline intervention compliance, dynamic (a) and control limit (b)

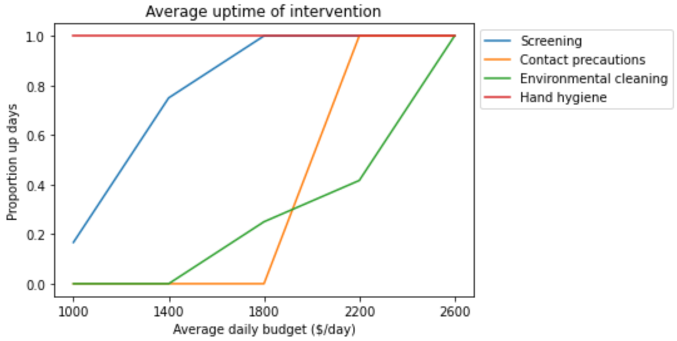
Policy	ICER (Reference: S)		
	Cost of infection = $12,000	Cost of infection = $24,000	Cost of infection = $9,000
$500, D	-141132	-129132	-144132
$500, CL	-147316	-135316	-150316
$400, D	-106054	-94054	-109054
$400, CL	-109159	-97159	-112159
$300, D	2814	14814	-186
$300, CL	2814	14814	-186
$200, D	3541	15541	541
$200, CL	2183	14183	-817

Baseline, including labor costs

To test the stability of the infection controls ranking apparent in Figure 9, we re-run the baseline community hospital MIPs with an expanded cost estimation. For these experiments, we include cost of hospital worker or clinician labor required for each infection control activity. For example, we consider the pay rate for environmental services staff for the average time they spend cleaning a hospital room. Figure 17 shows that the uptime of environmental cleaning is never greater than the uptime of screening at each budget for both the dynamic and control limit policies. Visualization of the optimal policies and summary of performance are included in the Appendix (Figure 27 and Table 28).



(a)

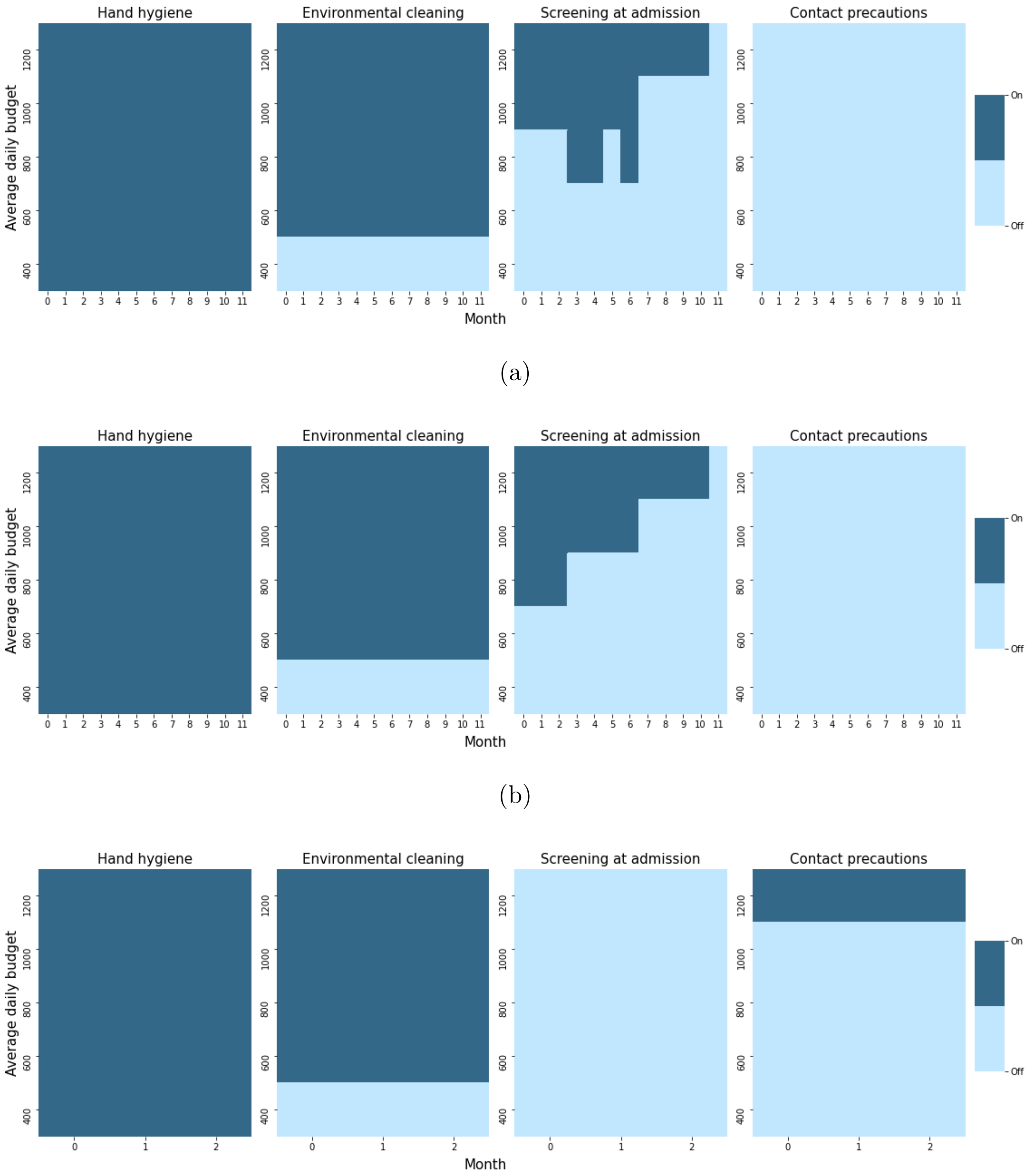


(b)

Figure 17: Optimal infection control policy uptime by budget for community hospital with labor included in costs, dynamic (a) and control limit (b)

5.4.2 Academic Hospital Model

Figure 18 displays the optimal policy under baseline conditions in the academic hospital model. Table 20 records the performance of each of the policies. Notably, the three types of policies are much more ‘similar’ than in the community hospital model, as evidenced by the small D/CL and CL/S gaps. This is further emphasized by the ICERs in Table 21, which show that it is only cost-effective to switch from the static policy if the cost of an individual CDI is particularly high. This suggests that there is diminished benefit to switching from a static policy to a dynamic/control limit policy in the academic hospital model. Additionally, in comparison to the community hospital model, the use of contact precautions is rarely optimal for any of the three policy types examined. Figure 19 plots the proportion of 'uptime' for each of the four infection control interventions under the academic hospital ABM. For the dynamic and control limit policies, these plots are identical, suggesting that the dynamic policy shifts some infection control uptime to later in the planning period. Also, similarly to the community hospital case, the uptime of screening at admission increases as the budget increases. Finally, like the community hospital case, both environmental cleaning and screening are used less than hand hygiene, which is optimal across all assessed budgets for the full planning period.



(a)

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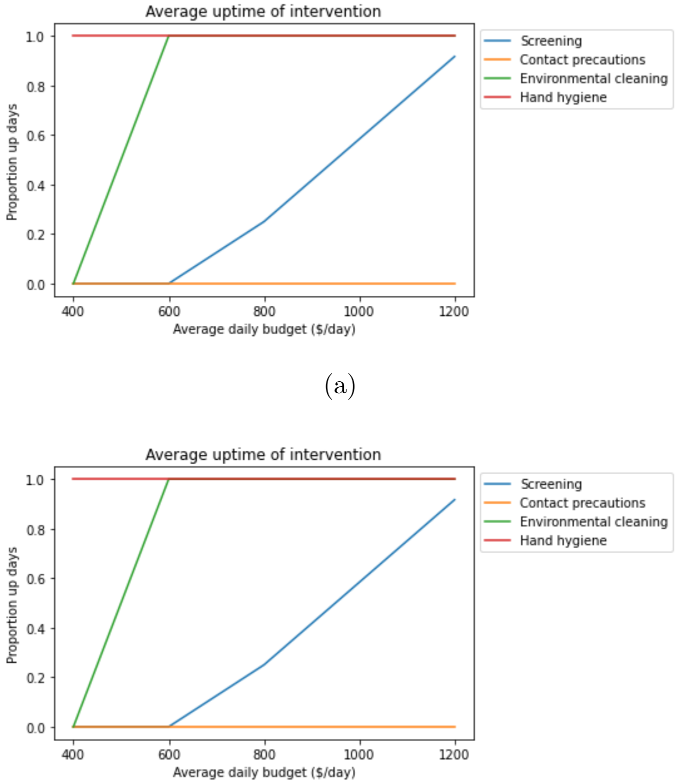
(c)

Figure 18: Optimal infection control policy, dynamic (a), control limit (b), and static (c)



(a)

(b)

Figure 19: Optimal infection control policy uptime by budget, dynamic (a) and control limit (b)

Table 20: HA-CDI rate and total cost by policy and budget, academic hospital model

Average daily budget ($)	HA-CDI/10000 Patient Days					Total Costs		
	Dynamic	Control Limit	Static	D/CL Gap	CL/S Gap	Dynamic	Control Limit	Static
1200	6.52	6.52	6.52	0.00%	0.00%	416010.8	416010.8	416010.8
1000	7.06	7.06	8.07	0.00%	12.56%	343518.1	391160.6	314556.4
800	7.62	7.63	8.07	0.04%	5.49%	267781.5	270797.3	213319.1
600	8.07	8.07	8.07	0.00%	0.00%	213370.6	213370.6	213370.6
400	10.62	10.62	10.62	0.00%	0.00%	156363.2	156363.2	156363.2

Table 21: Cost-effectiveness analysis, baseline academic hospital model

Policy	ICER (Reference: S)		
	Cost of Infection = \$12000	Cost of Infection = \$24000	Cost of Infection = \$9000
1200, D	-123648	-111648	-126648
1200, CL	-123648	-111648	-126648
1000, D	-16569	-4569	-19569
1000, CL	-16569	-4569	-19569
800, D	-110072	-98072	-113072
800, CL	-117776	-105776	-120775

5.4.3 Total exposures over time

Infectious diseases are often expected to spread very quickly under conditions of minimal infection control. This is certainly the case for airborne infectious diseases, such as Covid-19. However, for an infectious disease like CDI, which is transmitted via the fecal-oral route, it is not clear if this pattern in spread is reflective of reality. To investigate the behavior of CDI spread, we tracked the exposure rate in the academic hospital model over six months with minimal infection control. Figure 20 displays the estimated number of exposures each day in the academic hospital model. Although the number of daily exposures can vary dramatically day-to-day, the cumulative number of exposures (Figure 21) shows a generally constant increase in the total number of exposures.

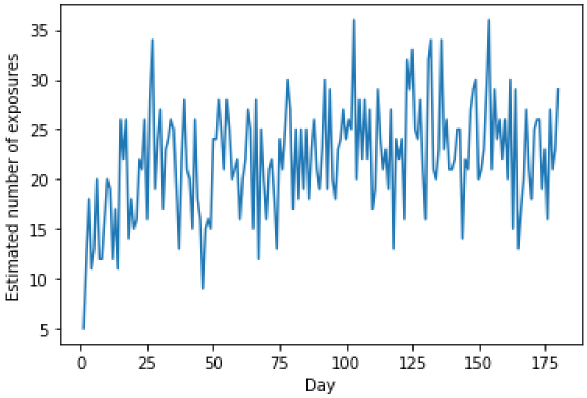


Figure 20: Daily estimate of exposures over approximately 6 months

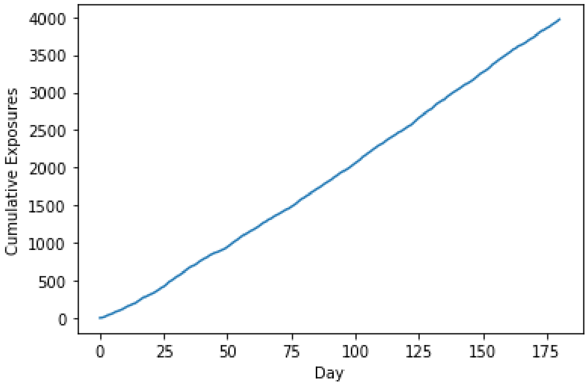


Figure 21: Cumulative number of exposures over approximately 6 months

5.5 Discussion

We solve our optimal control MIP M in various hospital conditions to assess changes in optimal infection control policies. Our results demonstrate three main findings of managerial interest to the infection control community.

The first insight is that control limit style policies can recover much of infection-preventing benefit of dynamic policies while maintaining a much simpler-to-implement structure. We also find that control limit policies consistently outperform static policies by roughly 10-28% for the community hospital baseline case. We also note that the largest CL/S gaps tend to occur in the middling budgets. This is intuitive, as it stands to reason that the greatest benefits of optimal decision making would be felt in the cases where resource allocation decisions are the least obvious. Additionally, it is often cost effective to switch from a static policy to a dynamic or control limit policy when considering the costs associated with an individual HA-CDI under a willingness to pay comparable with the cost of an infection. We note that there are several cases where the ICER associated with switching from a static to control limit is positive, indicating that the control limit policy saves both infections and cost. As evidenced by Tables 13, 16, typically a control limit policy is only cost effective is its associated CL/S gap is at least about 15%. Control limit and dynamic policies for a given budget band become more cost effective as the proportion of colonized, infected, or susceptible patients increases, or if the intervention baseline performance is worse. We also see that control limit policies retain their strong performance when implemented over a five year period. One explanation for this could result from the exposure rate behavior under weak infection control, as illustrated in Figure 21. If the CDI exposure rate does not accelerate under poor infection control, it is reasonable that rates of CDI remain low even after several infection control interventions have been rolled back.

The second insight from these results is that there exists a general ranking on when each infection control is added to the optimal bundle for control limit policies, with hand hygiene preceding environmental cleaning, which in turn precedes screening at admission. This insight contrasts with the cost-effectiveness analysis done in Barker, et al [161]. While the cost-effectiveness analysis 'ranks' (daily) environmental cleaning as the most cost-effective intervention, it is not the case from the MIP experiments that environmental cleaning should be the first intervention used. Clearly, because of the high cost of environmental cleaning and screening at admission, there is a certain budget threshold that must be obtained in order for these interventions to be used. Additionally, it is clear that contact precautions are typically only used at the very high budgets (when there is sufficient resources to simply implement all controls), or at the very low budgets (when there are little resources for anything else). As a result, contact precautions seem to act as a complement to other infection controls, and are generally only used when better options are either unavailable or already in-use. The region where contact precautions serve as a complement to other infection control interventions can vary, though it appears to be similar across the D and CL policies, under a specific hospital configuration. This finding contrasts somewhat with those from [63] and Chapter 3, which suggest that resources saved from deimplementing contact precautions may be better put towards other infection control interventions. In the case of the MIP, this re-allocation becomes less feasible and hence contact precautions are included in the optimal bundle more often. While the intervention ranking is only visible in the control limit policies, the uptime for each intervention in both the dynamic and control limit policies reflects this ranking too. This suggests that while such a ranking might not be apparent in the dynamic policy, there is an optimal 'amount' of each infection control, subject to policy type and hospital conditions.

When we expand the estimate of each element in the cost grid to include costs associated with hospital worker and clinician labor, we see a slightly different ordering to the interventions (Figure 17). In this case, screening tends to dominate environmental cleaning at each budget level. Including labor costs shifts the perspective from that of the infection control program to a higher-level hospital administrator responsible for budgeting for both infection control and employee salaries.

Our final insight from these experiments relates to the 'no free lunch' principle. When only considering the costs associated with providing infection control, we did not find any CL policies that are both cost- and infection-saving when compared to static policies. This is likely because the variable costs of infection control are too low to make a meaningful impact on overall costs in the cases we studied. Additionally, it does not seem likely that CDI grows at an exponential rate under relatively poor infection control policy (see Figure 21). This lack of exponential growth suggests that, although poor infection control policy has negative outcomes, there are fewer delayed costs in the context of CDI compared to other infectious diseases like Covid-19. However, when the cost of an individual HA-CDI is sufficiently high, there are indeed cases where the CL policy becomes cost- and infection-saving, or at least cost-effective for a willingness-to-pay similar to the cost of an infection. We note that any Medicare penalties through the HACRP likely constitute a larger burden on hospitals than the internal costs incurred by a single HA-CDI. We do not provide an estimate of Medicare penalties for CDI, but it is likely that such penalties will greatly increase the cost per HA-CDI, leading to more CL policies becoming cost effective for a willingness-to-pay of \$12,000 or less. Overall, to achieve lower rates of HA-CDI, it is likely that an infection control team will always need to spend more on infection control interventions, but this investment pays off when considering the costs of each infection.

There are many limitations to our optimal control model formulation and MIP approximation. Perhaps the most significant limitation of this modeling approach is the lack of stochasticity in the exposure rate and the disease state transitions. Given the highly stochastic nature of CDI spread, the exposure rate associated with a bundle of interventions is better represented with a probability distribution, rather than a point estimate. As a result, this could lead to deviations from the MIP-determined state path over the time horizon, which could result in the initial optimal solution becoming sub-optimal. The decision to model the exposure rate and transitions between state variables as deterministic is deliberate. We draw on the law of large numbers to support the assumption that over a sufficiently long period of time with a large number of disease transitions, the disease state transition rates approach their averages. Still, the actual trajectory of the state variables can vary from the MIP-projections. In such a case, the MIP can be resolved for the remaining time horizon and budget to obtain a new optimal policy. A stochastic optimization approach would be a natural extension to this work.

One such limitation is the lack of patient heterogeneity considerations. For example, we assume that the exposure rate can be applied to the entire susceptible population in the hospital. However, it is more realistic for the exposure rate to vary ward-by-ward. Including ward-level variations for exposure rate would involve significant expansion to the model. Likely, this could involve state constraints for each ward in the hospital, and all parameters would need to be estimated by ward. Such changes would likely make the optimal control model and the MIP approximation essentially impossible to solve, even for small instances. Because the ABM used to calculate exposure rate and costs may consider patient heterogeneity, we believe that the model hospital-wide estimates provide a reasonable estimate of average exposure rate. By using an ABM to inform our optimal control model, we shift the inherent system complexity from the optimization model to the ABM, which is better able to handle it.

Another limitation of this MIP model is the inability for the model to select intervention intensity between 'off' and 'on'. This could be accomplished by including an intermediate intervention intensity level in the creation of V (i.e., $h = 3$). This would lead to a much larger set of possible bundles, which could render the MIP nearly impossible to solve for even short planning periods. Another limitation of this study is the lack of current operating procedures to compare the MIP-produced policies against. As there is very little formal guidance given to infection control intervention programs in hospitals, there is an enormous variety of strategies used in hospitals across the United States.

Additionally, infection control can be highly dynamic in certain hospital environments. For example, if a hospital is approaching the end of its planning period with surplus resources, the hospital would most likely use those remaining resources for additional infection control. These resources could be directed towards some new intervention, or to strengthen an intervention already in place. This discretionary nature is difficult to capture in optimization modeling.

Another limitation of the model relates to the concept of using a MIP to approximate an optimal control model. Overall, the estimates of the number of infections obtained from the MIP is not reliable, as shown in the Appendix (Table 29). However, all the rates of HA-CDI and costs associated with each policy were derived directly from the ABMs, which are considered the 'gold standard' for estimating the impact of infection control policy. Additionally, the costs estimated by the MIP are larger than those estimated by the ABM, which suggests that the MIP estimate of costs is more conservative.

Nonetheless, because the MIP is an approximation with objective values that are not strong estimators of infection-related outcomes, there is still a possibility that other control limit or dynamic policies exist which outperform those described in this study. This limitation is fundamental to this type of grid based approximation for optimizing outcomes over a highly complex model like an ABM.

A final limitation of our MIP is the long solve time required to prove a near-optimal dynamic policy. For a fully dynamic policy with a planning period of 12 months, there exist on the order of 10^{17} possible policies. For the community hospital model MIPs, the model could easily take far more than 12 hours to reach a 1% optimality gap for dynamic policies. This problem persisted even after implementing a 'warm-start' approach, suggesting that using the MIP to develop these policies is not always practical. While the dynamic policies could never actually be implemented in a hospital setting, it is important to obtain high quality estimates of optimal policy performance in order to characterize the cost of a control limit or static policy. We minimized the MIP gaps as much as possible for the dynamic policies (see Appendix Table 30).

This study has revealed many opportunities for future research. One promising line of research would be to develop heuristic 'rules-of-thumb' for hospital infection control. While the optimal control model presented in this study does not admit a closed form solution, certain aspects of it are amenable to analysis. For example, according to the Maximum Principle, an optimal policy must maximize the Hamiltonian $\mathcal{H}(u, x^*, b^*, y, z, t)$ at each time t. The primary obstacle to computing a policy u that satisfies this criteria is the unknown values of the shadow prices y, z. However, it is possible to characterize these shadow prices using first or second order approximations. Another potential line of research would be to explore opportunities for using 'black box optimization' or machine learning methods to build infection control policies. One final line of research that might allow for use of the MIPs developed in this chapter would be to develop pairwise comparisons of each infection control intervention in order to create a ranking. This ranking cannot provide a specific policy, but can be arguably even more valuable to infection control professionals. A pairwise approach would likely result in a much easier to solve MIP, with smaller optimality gaps. The development of such a ranking is not common in the operations research literature, and could be one of the few (if only) studies to take such an approach.

Overall, the work presented in this chapter is among the first across both the medical and operations research/management science literature to explore the characterization of optimal policies to control hospital-associated infections. This particular problem does not exhibit much of the traditional structure that makes many healthcare operations research problems tractable. However, this opens up many opportunities for further novel modeling techniques.

Chapter 6

Conclusions

6.1 Summary

This dissertation presents four different studies focused on limiting the burden of *C. difficile* infection in hospitals. In the second chapter, we describe the need for interventions targeting CDI patients living in disadvantaged neighborhoods. We find that disparities in CDI-related outcomes are significant even when controlling for indicators of individual income, thereby suggesting a strong effect attributable to a patient's regular environment. Implementing such interventions may help to prevent additional downstream infections upon readmission. While social determinants of health have been studied extensively, our study is one of the very few to examine CDI and neighborhood disadvantage.

The third chapter demonstrates that there is little association between visitor contact precautions (VCPs) and reduction in HA-CDI. We find that VCPs are associated with very little reduction in HA-CDI, even under cases that theoretically should lead to the highest impact of VCP. We also find that very small improvements to the compliance with other infection control protocols (such as hand hygiene), are associated with a larger reduction in HA-CDI than significant improvements to VCP. Overall, de-implementing VCPs can potentially free up resources for more impactful infection control interventions.

The fourth chapter describes the creation of an agent based simulation of CDI in an academic hospital setting. By estimating parameters from primary hospital data and recreating the hospital layout and behavior, we are able to replicate actual CDI trends from 2013-2018. We also found that hospital-specific modeling can reveal discrepancies in the performance of infection control interventions, compared to a generic hospital model. These discrepancies likely arise from hospital-specific features, such as the physical layout and staff behavior patterns. While future work is needed to refine this model, it can serve as a novel tool for understanding the relative impact of different infection control measures.

The fifth chapter focuses on formulating and solving an optimal control model to develop infection control policies. The model in this section is one of the only to investigate optimal policies for controlling HA-CDI subject to a strict budget constraint. The budget constraint used in this model is a global budget, which contrasts with the per-time step budget constraint that is much more common in the operations research literature. This global budget is highly important to the problem context, as infection control policies are typically planned and budgeted over a set period (often one year). As a result, the MIP approximation to the optimal control model was highly difficult to solve to optimality. However, we were still able to obtain three managerial insights from the study. The first insight is that control limit style policies recover much of the benefit of full dynamic policies, and are much simpler to implement. The second insight is that there exists a general ordering to when interventions are added to the optimal infection control bundle. This ranking remained consistent even as the proportion of colonized, infected, and susceptible patients changed. Finally, we demonstrated that there is 'no free lunch' in hospital infection control. This is likely the result of the fact that CDI rates do not accelerate under minimal infection control. Because of this, infection control policies are not effective at 'heading-off' a CDI surge, and typically higher spending will result in better outcomes. These findings suggest that perhaps the best way for hospitals to reduce rates of CDI is to simply fund infection control programs.

While all the studies presented in this dissertation have limitations, we believe this work represents an important early step into developing hospital infection control policies from an optimization and modeling perspective.

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Appendix A

A.1 Chapter 2 Appendix

Table 22: Odds of 30-day readmission for CDI patients by ADI score national percentile

Variable	Odds ratio (95% CI)	Predicted Probability (95% CI)
Unadjusted		
ADI <85 percentile	Reference	21.3 (20.7, 21.9)
ADI 85 percentile	1.32 (1.20, 1.45)	26.3 (24.5, 28.1)
Adjusted		
Patients		
Neighborhood disadvantage		
ADI <85 percentile	Reference	21.6 (21.0, 22.2)
ADI 85 percentile	1.16 (1.04, 1.28)	24.1 (22.4, 25.8)
Age		
65+ y	Reference	21.5, (20.8, 22.2)
18-65 y	1.14 (1.01, 1.29)	23.8, (22.0, 25.6)
Sex		
Male	Reference	22.0, (21.0, 23.0)
Female	0.99 (0.92, 1.07)	21.9, (21.1, 22.6)

Table 22 continued from previous page

Variable	Odds ratio (95% CI)	Predicted Probability (95% CI)
Race		
White	Reference	21.8, (21.1, 22.4)
Black	1.08 (0.96, 1.20)	23.0, (21.3, 24.7)
Other/Unknown Race	0.98 (0.76, 1.26)	21.6, (19.6, 23.6)
Medicaid Enrollment		
No Medicaid in past 12 months	Reference	21.2, (20.5, 21.9)
Medicaid in past 12 months	1.15 (1.06, 1.25)	23.6, (22.4, 24.8)
Disability		
Not disabled	Reference	21.6, (20.8, 22.4)
Disabled	1.05 (1.16, 1.00)	22.5, (21.2, 23.8)
Patient RUCA		
Urban	Reference	22.2, (21.5, 22.9)
Suburban	0.87 (0.77, 0.99)	20.0, (18.0, 21.9)
Large rural	0.85 (0.67, 1.09)	20.9, (19.1, 22.7)
Small rural	1.11 (0.75, 1.65)	22.8, (20.7, 24.9)
Elixhauser comorbidities		
Hypertension	1.06 (0.96, 1.17)	22.1, (21.4, 22.7)
Fluid and electrolyte disorders	1.12 (1.03, 1.22)	22.6, (21.8, 23.4)
Deficiency anemia	1.13 (1.04, 1.23)	22.8, (22.0, 23.6)

Table 22 continued from previous page

Variable	Odds ratio (95% CI)	Predicted Probability (95% CI)
Diabetes (without chronic complications)	1.06 (0.97, 1.15)	22.5, (21.5, 23.5)
Renal failure	1.19 (1.10, 1.29)	23.7, (22.6, 24.8)
Chronic pulmonary disease	1.04 (0.96, 1.12)	22.3, (21.3, 23.3)
Congestive heart failure	1.04 (0.95, 1.13)	22.3, (21.2, 23.4)
Depression	1.02 (0.94, 1.11)	22.2, (21.0, 23.3)
Other neurological conditions	1.02 (0.94, 1.11)	22.2, (21.0, 23.4)
Hypothyroidism	0.99 (0.91, 1.08)	21.8, (20.6, 23.0)
Peripheral vascular disease	1.08 (0.99, 1.17)	22.9, (21.6, 24.1)
Weight loss	1.00 (0.92, 1.09)	22.0, (20.7, 23.2)
Obesity	1.03 (0.94, 1.13)	22.3, (21.0, 23.7)
Diabetes (with chronic complications)	1.12 (1.01, 1.25)	23.5, (21.9, 25.1)
Valvular disease	1.02 (0.93, 1.13)	22.3, (20.7, 23. 8)
Metastatic cancer	1.03 (0.86, 1.23)	22.3, (19.4, 25.3)
Alcohol abuse	1.13 (0.96, 1.33)	23.9, (21.1, 26.7)
Drug abuse	1.39 (1.18, 1.64)	27.6, (24.5, 30.7)
Chronic blood loss anemia	1.06 (0.90, 1.25)	22.8, (20.1, 25.6)
Lymphoma	1.22 (1.01, 1.48)	25.3, (21.9, 28.8)
Acquired immune deficiency syndrome	1.00 (0.68, 1.49)	22.0, (15.4, 28.6)

Table 22 continued from previous page

Variable	Odds ratio (95% CI)	Predicted Probability (95% CI)
Pulmonary circulation disease	1.06 (0.94, 1.19)	22.8, (20.9, 24.6)
Rheumatoid arthritis	1.20 (1.06, 1.35)	24.8, (22.6, 26.9)
Paralysis	1.04 (0.91, 1.18)	22.5, (20.4, 24.5)
Liver disease	1.15 (1.00, 1.31)	24.1, (21.8, 26.3)
Solid tumor without metastasis	1.02 (0.91, 1.14)	22.2, (20.4, 24.0)
Psychoses	0.93 (0.83, 1.04)	20.9, (19.2, 22.5)
Coagulopathy	1.10 (1.00, 1.22)	23.3, (21.8, 24.9)
Index stay		
Length of stay		
2 days	Reference	19.0, (17.0, 21.0)
3-4 days	1.13 (0.97, 1.32)	20.9, (19.6, 22.2)
5-6 days	1.25 (1.07, 1.46)	22.6, (21.2, 23.9)
7+ days	1.24 (1.08, 1.43)	22.5, (21.7, 23.3)
SNF Discharge		
Not discharged to SNF	Reference	21.3, (20.6, 22.1)
Discharged to SNF	1.10 (1.02, 1.18)	22.9, (21.9, 23.9)
Index Hospital		
Medical school affiliation		
No medical school affiliation	Reference	21.9, (21.0, 22.8)
Minor Medical School affiliated	0.92 (0.84, 1.01)	20.5, (19.4, 21.7)

Table 22 continued from previous page

Variable	Odds ratio (95% CI)	Predicted Probability (95% CI)
Major Medical School affiliated	1.07 (0.98, 1.17)	23.1, (22.0, 24.2)
Hospital type		
Non-profit/Government	Reference	22.0, (21.4, 22.6)
For profit	0.96 (0.86, 1.06)	21.3, (19.6, 22.9)
Discharge volume		
Discharge volume tertile 1 (highest)	Reference	22.2, (21.5, 22.9)
Discharge volume tertile 2 (middle)	0.95 (0.87, 1.04)	21.3, (20.1, 22.6)
Discharge volume tertile 3 (lowest)	0.83 (0.61, 1.15)	20.7, (18.3, 23.1)

Table 23: Sensitivity analysis of risk of readmission by ADI grouping for varying threshold (Reference: patients below threshold)

ADI Threshold	Adjusted Odds ratio (95% CI)
95	1.07 (0.89, 1.27)
85	1.16 (1.04, 1.28)
75	1.14 (1.05, 1.25)
65	1.14 (1.05, 1.23)
55	1.10 (1.02, 1.19)
50	1.11 (1.03, 1.19)
45	1.08 (1.00, 1.16)
35	1.05 (0.97, 1.14)
25	1.04 (0.96, 1.14)
15	1.05 (0.94, 1.17)
5	1.01 (0.83, 1.23)

Table 24: Odds of 30-day rehospitalization by subgroup

	Not discharged to SNF	Discharged to SNF	Not Medicare-Medicaid dual enrolled	Medicare-Medicaid dual enrolled	White	Black	Other/ Unknown
	Adjusted OR (95% CI)		Adjusted OR (95% CI)		Adjusted OR (95% CI)		
ADI <85 percentile	Reference	Reference	Reference	Reference	Reference	Reference	Reference
ADI $\leq$ 85 percentile	1.19 (1.05, 1.35)	1.04 (0.88, 1.24)	1.20 (1.04, 1.38)	1.11 (0.95, 1.29)	1.19 (1.04, 1.36)	1.04 (0.84, 1.28)	1.25 (0.93, 1.69)
Ratio of Odds Ratios (95% CI)	1.14 (0.92, 1.41)		1.08 (0.88, 1.34)		White & Black: 1.15 (0.90, 1.47) White & Other/Unknown: 0.95 (0.68, 1.31)		

A.2 Chapter 3 Appendix

Representing patient disease state

Patient Clostridioides difficile infection (CDI) state is modeled using a discrete-time Markov chain containing nine states, as described in eTable 1. The states of death and non-susceptible are absorbing, from which patients cannot transition to any other state. Possible transitions between disease states are illustrated in the eFigure.

Input parameters for the baseline model configuration

All infection control interventions included in the agent-based simulation model can be implemented at multiple levels representing varying compliance with protocols. Interventions can be implemented at the baseline level, representing minimal (if any) institutional support, and therefore have the least agent compliance. Interventions can also be implemented at an ideal level, representing significant institutional support and agent compliance. The simulation model includes several parameters to describe the baseline state, distribution, and behavior of agents in the model. The parameters that were directly referenced or altered in our study of VCPs de-implementation are described in eTable 2. For a full description of the model's input parameters and their derivations, please see Barker, et al 2018 [20].

Detailed description of visitor behavior

Visitors may enter the simulation between the in-model hours of 9:00am and 9:00pm. When visitor agents are initialized, they are assigned a length of stay according to an exponential distribution with a mean of 15 minutes. While the visitor is in the patient room, healthcare workers may enter and interact with the patient and the environment, but not with the visitor. After the visitor has completed their stay, probabilities for patient-to-visitor and environment-to-visitor contamination trials are calculated, depending on the visitor length of stay, frequency of contact, proportion of the room or patient that may harbor C. difficile spores, and the transfer efficiency between surfaces. The proportion of the room or patient harboring C. difficile depends on the patient's disease status. If either of these probability trials are successful, the visitor is considered contaminated.

Right before leaving the patient room, Bernoulli trials are used to determine if the patient washed their hands upon exit or was wearing VCPs during their stay. These trials are dependent on the compliance and effectiveness of the two interventions. If either trial is successful, the visitor is no longer considered contaminated. The visitor moves to the ward common ward, where they remain for five minutes. The model then calculates the probability for a visitor-to-environment contamination trial, depending on visitor length of stay, frequency of contact, and transfer efficiency between surfaces. If the trial is successful and the visitor was contaminated, high touch surfaces in the common room are considered contaminated. The visitor is then removed from the model. Conversion of model from NetLogo to Java

The NetLogo model described in Barker, et al simulates the spread of hospital onset Clostridioides difficile infection (HO-CDI) in a generic, 200-bed acute care hospital [20]. Though NetLogo's ease of use and graphical interface are highly useful features in modeling infectious diseases, other programming languages can offer greater flexibility and speed. Java is one such language and lends itself naturally to agent-based modeling because of its object-oriented capabilities. To enable the experiments described in this paper we first converted the model described in Barker et al to an analogous model in Java (version 8); see the Appendix material of Barker et al for detailed logic governing agent and environment interactions [20].

Coding and debugging of the Java model was completed in Eclipse IDE v4.8 (Photon), developed by the Eclipse Foundation. The Java model replicates the agent and environmental variables and behavior, with changes made as necessary to accommodate Java data structures and objects. Both the NetLogo and Java models use the Colt Project's Mersenne Twister algorithm to produce random number generator streams. ETables 3 and 4 compare the output of the NetLogo and Java models for different infection control measures implemented at the enhanced and ideal levels, respectively. Of primary interest was the percent change in HO-CDI per 10000 patient days and colonizations per 1000 admitted patients as a function of different infection control implementation. Absolute percent changes of less than one percent were considered insignificant. Like the NetLogo model, the Java model was face validated by subject matter experts in hospital associated infections and simulation.

To determine stability of results, HO-CDI per 10000 patient days and colonizations per 1000 admitted patients were examined as a function of number of replications, as seen in eTable 5. As the Java model showed a similar stability at 5000 replications to the NetLogo model, we concluded that 5000 replications were sufficient to produce stable results.

A.3 Chapter 4 Appendix

A.3.1 H-ABM Logic and Assumptions

H-ABM draws upon previously published ABMs of the spread of hospital-associated C. difficile in a generic hospital model, particularly Codella (2015), and Barker (2018)1,2. These models replicate the events and conditions related to the spread of C. difficile in a small, community-hospital type setting. To create H-ABM, we expanded this generic model considerably, but maintained several of the modeling logic and assumptions from the generic model. C. difficile propagation In both H-ABM and the generic model, a patient develops CDI via exposure to C. difficile spores. Once a patient has been exposed, the progression of CDI follows from the DTMC. Patients may be exposed to C. difficile spores through interactions with contaminated agents (i.e., doctors, nurses, visitors, and other patients), or environments. The H-ABM and generic model simulates each of these types of interactions explicitly, and conducts Bernoulli "coin-flip" trials to assess the success of exposure if one of the interacting agents/environment is contaminated with C. diff spores. Probability of exposure increases with length of interaction and the rate of physical contact. For example, we model the probability that a nurse whose hands are currently contaminated with C. difficile spores will expose a patient to C. difficile by the following equation.

$$p_{np} = (1 - exp(-\lambda_{np} LOS_n))\alpha_{np}$$

Where,

p_{np} = Probability for nurse-to-patient exposure without infection control intervention

λ_{np} = Rate of contact between patients and nurses

LOS_n = Length of stay of nurse in patient room

α_{np} = Transfer efficiency of *C. difficile* between hands.

H-ABM uses p_{np} and the probability of success for the relevant infection control intervention to determine if *C. difficile* is propagated. To expand the example above, the model then follows the procedure illustrated below, where PHH represents the probability of a successful patient hand hygiene event (i.e., the product of patient hand hygiene compliance and effectiveness):

1. Generate two random numbers on interval $[0, 1]$: designate as $r1, r2$
2. Assess if $r_1 \leq p_{np}$ AND $r_2 \leq PHH$
3. If TRUE, exposure successful; else, exposure unsuccessful.

If exposure is successful, the patient disease state is updated to the "Exposed" state illustrated in Figure 1, then updated every six hours in-simulation according the DTMC transition probability matrix. Similar computations are used to assess contamination in each agent/environment interaction. Interactions with the environment are not explicitly modeled and are assumed to occur with infinite contact rate. Therefore, probability of transmission of C. difficile spores via environment is dependent only on duration of stay in a particular environment. Appendix Figure A1-A3 illustrate the logic used to update each type of agent in the H-ABM and the generic model, including relevant interactions with other agents. C. difficile infection transition probability matrix The H-ABM and the generic model use a time step of 5 minutes in-simulation. Every six hours in-simulation, the disease state of each patient is updated according to a discrete-time Markov Chain (DTMC). The DTMC transition probability matrix used in the H-ABM governs the transitions illustrated in Figure 1 of the manuscript and is one of 10 candidate matrices developed in Codella, et al. These 10 matrices were produced by calibrating the generic hospital model to historical CDI rate data and selecting the best performing matrices, as evaluated by mean percentage error across multiple outcomes of interest1. We emphasize that all transitions shown with solid arrows Figure 1 are independent of the hospital state and the infection control interventions in place. The two exceptions are detailed below:

1. Non-susceptible to susceptible: this transition is only possible if a patient begins a course of antibiotics during their stay in the hospital. Therefore, patient agents that start a course of antibiotics are updated to the 'susceptible' state when their antibiotics start.

2. Susceptible to exposed: this transition is only possible if a patient is exposed to C.difficile spores through interaction with another agent or the environment. The prevalence of C. difficile in the hospital, which is affected by infection control interventions, is the primary driver of this transitions. Patients transition to 'exposed' as soon as an exposure occurs in the simulation.

A.3.2 Description of primary hospital data

The data used to build the H-ABM and estimate infection control intervention parameters was obtained from two sources: a database of patient electronic health records, and the records of the target hospital's infection control program. From the database of target hospital patient electronic health records, we obtained summary statistics across 157,507 patient admissions from the years 2013-2018 (inclusive). We only considered records from patients over the age of 18 who were admitted as inpatients. From this dataset, we obtained the following counts, aggregated by each year and by each ward in the target hospital:

- Total number of admissions,
- Total number of patients over the age of 65 years,
- Total number of patients given a high-risk antibiotic (clindamycin, ceftriaxone, carbapenems, or fluoroquinolones) during their stay,
- Average length of stay,
- Total number of patients with an active high-risk antibiotic (clindamycin, ceftriaxone, carbapenems, or fluoroquinolones) prescription on admission.

We define an antibiotic as 'given' if there is a medication administration record (MAR) containing one of the following codes: These fields were delivered by the target hospital's translational research data team. No patient-identifying data was delivered or used in this study. The second source of data was the target hospital's infection control program, which records counts of the number of observed hand-hygiene events across

Table 25: MAR codes

MAR Code	Description
1	Given
6	New Bag
7	Restarted
9	Rate Change
12	Bolus
13	Push
100	Due
104	Bolus from Bag/Injection
106	Restarted IV
113	Continue from OR/PACU/Procedure
150	Given Early
151	Given Late
157	Downtime New Bag/Injection
158	Downtime Given
159	Documented in Another Care Area
166	Change Bag/Injection
175	Bolus
176	Bolus from Bag/Injection

the target hospital every month. The infection control program provided the following data, aggregated by the year (for 2013-2018, inclusive) and by each ward in the target hospital:

- Number of Hospital-associated CDIs per 10,000 patient days,
- Number of hand hygiene events recorded, performed by doctors,
- Number of hand hygiene events recorded, performed by nurses,
- Number of hand hygiene events recorded using alcohol-based hand sanitizer rub, performed by doctors,
- Number of hand hygiene events recorded using alcohol-based hand sanitizer rub, performed by nurses,
- Number of hand hygiene events recorded using soap-and-water, performed by doctors,
- Number of hand hygiene events recorded using soap-and-water, performed by nurses.

From these counts, we obtained probabilities of doctor/nurse compliance with hand hygiene practices for each year. We also obtained probabilities for use of alcohol-based hand sanitizer rubs vs soap-and-water for each hand hygiene event, for both nurses and doctors. As this data is proprietary, we aggregate the estimates of nurse and doctor hand hygiene compliance as “health care worker” hand hygiene compliance for presentation in this study. However, the H-ABM uses separate doctor and nurse hand hygiene compliance and effectiveness parameters.

A.3.3 Further changes in H-ABM

Barker, et al and Codella, et al previously published two generic models of hospital-associated CDI in adults [20, 94]. To create H-ABM we drew upon several of the assumptions inherent in previous models and introduced new structures. The first major difference between the Barker, et al model and the H-ABM is the programming language used to create each model. The Barker, et al model was built in NetLogo, but the H-ABM was created in Java. Java is a very flexible programming language and allows us to run replications of the H-ABM relatively quickly. A detailed description of the NetLogo to Java translation is included in Scaria, et al [63].

Another of these changes is the update to modeled hospital layout. Barker, et al models a hospital comprising 10 wards, each with 20 patient rooms. To mirror the layout of the target hospital, H-ABM comprises 18 wards of heterogeneous size, ranging from 8 to 41 patient rooms. To obtain an accurate representation of the target hospital, a research group member performed a walk-through of the hospital and recorded the number of patient rooms and common areas. The generic models assume that each ward has exactly one doctor's common room, one nurse's common room, and one visitor's/patient's common room. H-ABM allows for multiple common rooms of any type in each ward, and includes additional common areas shared by nurses and doctors, where applicable. Rooms for patients with negligible CDI risk (e.g., psychiatry, sleep studies), those that primarily serve outpatients, or that are sporadically occupied (e.g., rooms reserved for incarcerated patients) were omitted from the model. Healthcare worker common areas typically visited only at the beginning or end of a working shift, such as locker rooms, were omitted from the model. Hallways and other areas between patient rooms were also omitted from the model because of the short agent length of stay in these areas.

In the H-ABM, patients are admitted to the hospital wards according to a probability distribution created from historical target hospital admissions data. We assume that patients staying in a ward are admitted to the hospital for needs corresponding to the ward's specialty and use these specialties to help assess the CDI risk of those patients. Depending on the demographics, antibiotic use, and risk associated with each ward's specialty, patients are assigned as susceptible, colonized, infected, or non-susceptible upon admission. Length of stay varies depending on the patient's home ward. The H-ABM also adjusts patient susceptibility depending on whether a patient is taking an antibiotic associated with risk of CDI on the second day of their hospital stay.

The H-ABM also includes enhanced intervention logic for particular wards. The section of patient rooms for palliative care within a single ward requires healthcare workers to perform hand hygiene before entry. Also, following the infection control improvements made in 2016, bone marrow transplant patients were screened for CDI upon admission to the hospital; this translates to testing all patient agents assigned to a specific ward in the H-ABM at admission. To account for variation in healthcare worker hand hygiene across wards, we used by-ward historical rates of hand hygiene to estimate by-ward hand hygiene multipliers to modify hand hygiene parameters.

Because primary data pertaining to environmental cleaning compliance was not available, we needed to estimate parameters with a combination of estimates from literature and hospital data of other interventions. To account for the uncertainty in these estimates, we split the parameters of terminal and daily cleaning compliance into three parameters describing the minimum, maximum, and average compliances. For each environmental cleaning event, we sampled the probability of success (i.e., a cleaning event occurs and successfully removes C. difficile spores) from a symmetric triangular distribution parametrized by the minimum, maximum, and mean compliance estimates.

Two of the most important risk factors for developing CDI are general susceptibility (usually caused by advanced age, immunosuppression, etc.), and antibiotic use. In order to incorporate how the antibiotic prescribing practices and the susceptible population change over time, we used primary hospital data to obtain estimates for the proportion of patients susceptible to CDI and the proportion of patients who are administered antibiotics during their stay. These proportions varied over the years, with antibiotic use showing a marked decline in the target hospital.

A.3.4 CDI testing algorithm and infection control interventions

In response to high HA-CDI rates in 2013 and 2014, the target hospital initiated several new infection control interventions beginning in 2015 and 2016. In particular, the hospital implemented a novel CDI testing algorithm in 2015 to reduce the number of false classifications of HA-CDIs. The Centers for Disease Control and Prevention (CDC) guidelines classify all CDI cases tested positive within three days of admission as CA-CDI and any cases diagnosed after this time as HA-CDI. The new CDI testing algorithm promotes increased CDI testing during the first 48 hours of a patient's stay. The algorithm also encourages clinicians to consider alternate causes of gastrointestinal symptoms prior to testing after 48 hours of a stay and limits the number of diagnostic tests to one test every seven days.

The CDI Testing Algorithm was implemented in the target hospital towards the

Table 26: Input parameters unchanged from Barker, et al 2018 (Adapted from Scaria, et al 2021)

Admission Parameters	
Parameter	Mean value
Proportion of asymptomatic colonized patients	6.10%
Proportion of patients with CDI	0.29%
Health care worker behavior and distribution	
Parameter	Value
Patient-nurse contact probability [rate]	0.358 (for 5 minutes) [10.53 contacts/ minute]
Patient-doctor contact probability [rate]	0.688 (for 5 minutes) [9.25 contacts/ minute]
Number of nurses per 20 patient rooms	4
Number of doctors per 20 patient rooms	2
Average nurse service time	4.7 minutes
Average doctor service time	10.8 minutes
Average number of nurse visits per 6 hours	5
Average number of doctor visits per 6 hours	1
Visitor behavior	
Parameter	Mean value
Probability of receiving visitors (per day)	0.5
Number of visitors per visit	2
Visitor length of stay	15 minutes
Visitor-environment contact probability [rate]	0.932 (for 15 minutes) [0.179 contacts/ minute]

end of 2015. The testing algorithm was proposed and created after an extensive chart review found several patients had either been inappropriately tested for CDI (e.g., had gastrointestinal symptoms, but were taking laxatives). Inappropriately tested patients not only strain the hospital's laboratory resources and receive unnecessary antibiotic treatment, but could also lead to asymptomatic colonizations (which are not typically reported by hospitals) being classified as HA-CDIs [162, 163]. The chart review also revealed that several patients had gastrointestinal symptoms at admission, but were tested late into their stay. These patients tested late might have been exposed to C. difficile in the community and might have been classified as CA-CDIs instead of HA-CDIs. Late testing may also delay important treatment and lead to increased spread of C. difficile spores. These inappropriate and/or late tests caused the rate of HA-CDI to be inaccurately high. Since large academic hospitals can be penalized by the Centers for Medicare & Medicaid Services for high HA-CDI rates, reporting accurate HA-CDI rates is of great importance [164].

To represent the CDI testing algorithm in our model, we needed to estimate the number of patients tested in the hospital whose gastrointestinal symptoms had non-CDI causes (such as laxative or stool softener use). We assumed that community and hospital prevalence of non-CDI gastrointestinal symptoms did not change during 2013-2018. We also assumed that count of CDI tests in the years 2013-2015 includes patients that were inappropriately tested; similarly, we assumed that the count of CDI tests for the years 2016-2018 does not include inappropriately tested patients. We estimated the proportion of these inappropriately tested patients using the numbers of CDI tests administered within 48 hours of a patient's stay before and after the testing algorithm was implemented in late 2015. Similarly, we estimated the proportion of patients with

CDI that might have non-CDI related causes for their gastrointestinal symptoms using the change in the number of tests administered after 48 hours of a patient's stay before and after algorithm implementation.

Additional measures implemented in 2015 including a fluoroquinolone restriction in the trauma and solid organ transplant wards; screening asymptomatic bone marrow transplant patients upon admission; increased use of supplemental ultraviolet disinfection following all CDI discharges and transfers; deployment of ultraviolet disinfection in some non-CDI rooms [165]. Moreover, in 2016, the target hospital devoted additional resources to improving infection control intervention compliance. For example, hospital infection control started a program of direct observations for contact precautions and hand hygiene to improve adherence.

A.3.5 Parameter estimation

Intervention parameters in H-ABM are estimated through a combination of primary hospital data and literature. Since 2012, the target hospital has kept a record of hand hygiene compliance for nurses and doctors. This record differentiates between alcohol-based hand rub (ABHR) and soap & water hand hygiene events. This primary data was self-reported and likely overrepresents the compliance with hand hygiene protocols. To mitigate the effects of overrepresentation, we assumed the hospital hand hygiene data represents the rate of hand hygiene compliance of nurses and doctors when interacting with a known CDI patient.

To obtain estimates for all other intervention parameters, we needed to scale estimates drawn from literature using hospital hand hygiene data. The equation used to obtain scaled parameter estimate (i,j) for year i and intervention j is shown below.

$$\text{Scaled estimate}(i,j) \;=\; \frac{\text{Average}_w(ObsnurseHH(i), ObsdoctorHH(i)) \times Base(i,j)}{Average_w(Base\ nurse\ HH\ (i), BasedoctorHH(i))}$$

Obs = observed, HH = hand hygiene Where,

1. $Average_w(Obs\ nurse\ HH\ (i),\ Obs\ doctor\ HH(i))$ is the weighted average of observed healthcare worker hand hygiene compliance derived from hospital hand hygiene data,
2. $Average_w(Base\ nurse\ HH\ (i), Base\ doctor\ HH)$ represents the weighted average healthcare worker hand hygiene compliance when interacting with known CDI patients, as estimated from literature, and
3. *Base*(i,j) is an unscaled value of the parameter for year i and intervention j, as estimated from literature.

A.3.6 Intervention Performance in H-ABM

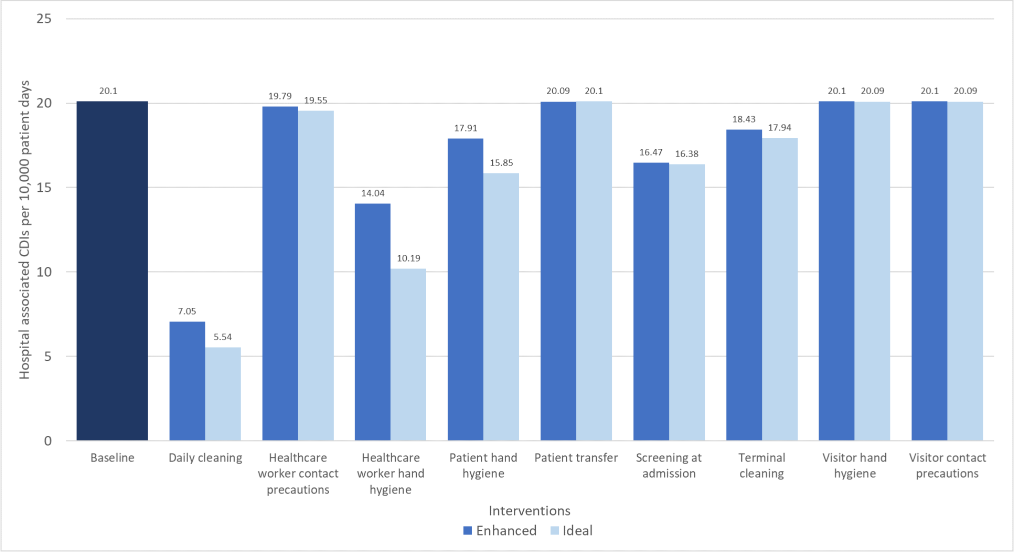


Figure 22: Rate of HA-CDI per 10,000 patient days for each intervention vs baseline

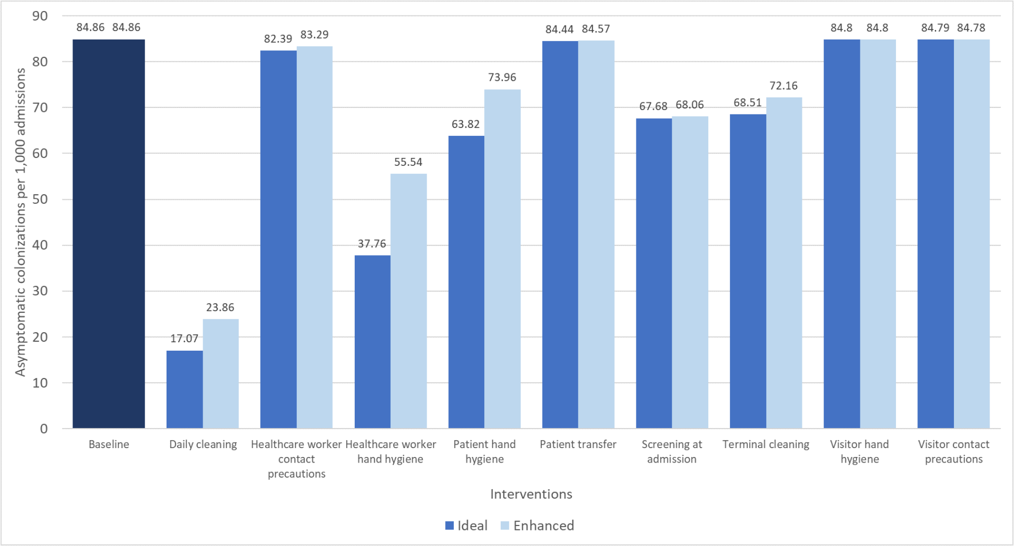
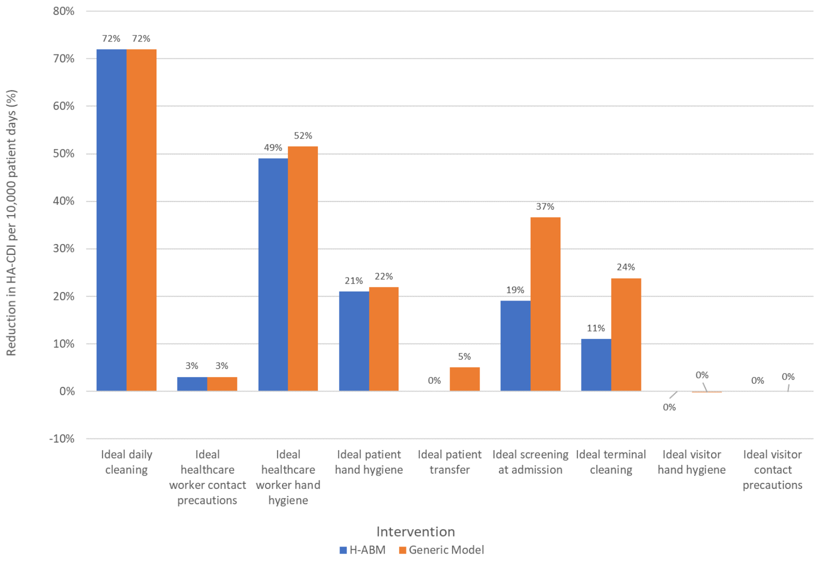
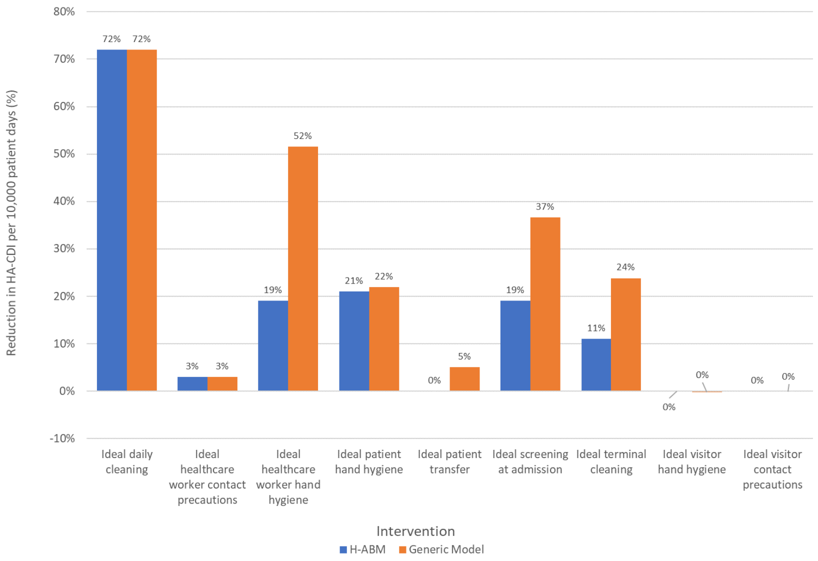


Figure 23: Rate of asymptomatic colonization per 1,000 admissions for each intervention vs baseline

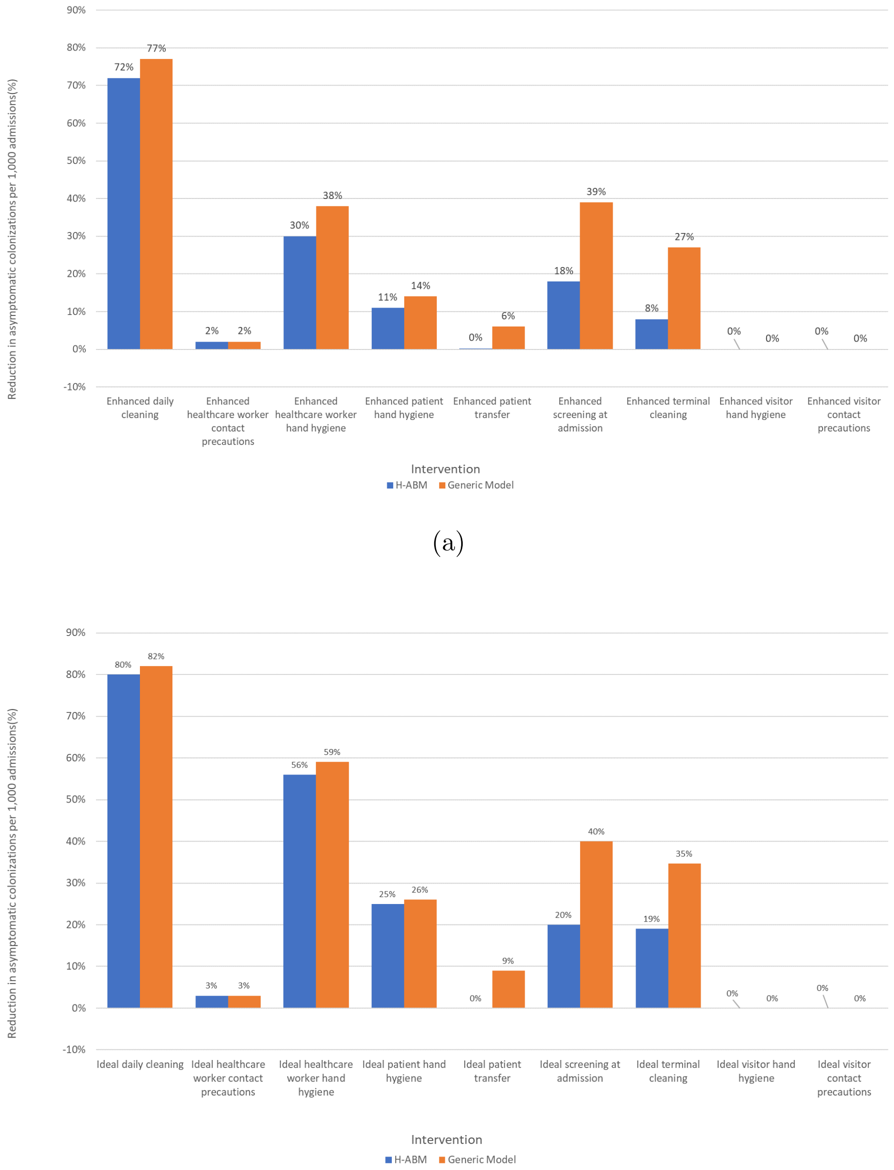


(a)



(b)

Figure 24: Enhanced (a) and ideal (b) single intervention reduction in HA-CDI per 10,000 patient days, H-ABM vs generic model



(a)

(b)

Figure 25: Enhanced (a) and ideal (b) single intervention reduction in asymptomatic colonizations per 1,000 admissions, H-ABM vs generic model

A.3.7 Sensitivity Analyses

Table 27: Rate of HA-CDI per 10,000 patient days by transition probability matrix vs historical rate of HA-CDI per 10,000 patient days from target hospital

Year	Transition matrix number										Actual CDI Rate
	1	2	3	4	5	6	7 (Baseline)	8	9	10	
2013	16.16	11.76	16.91	14.10	17.02	12.40	14.46	10.34	14.78	15.97	12.14
2014	16.57	12.06	17.27	14.48	17.38	12.70	14.80	10.56	15.14	16.39	13.70
2015	15.00	10.97	15.77	13.15	16.11	11.63	13.47	9.71	13.84	14.81	14.01
2016	7.87	5.96	8.58	7.00	9.03	6.42	7.23	5.47	7.60	7.80	7.58
2017	6.29	4.88	6.84	5.65	7.22	5.20	5.83	4.55	6.16	6.26	5.78
2018	6.11	4.74	6.59	5.53	6.98	5.07	5.68	4.43	5.98	6.09	6.43

A.4 Chapter 5 Appendix

A.4.1 Conditions for monotonicity

As demonstrated in the existing literature, non-linear optimal control systems rarely if ever display properties of monotonicity [152, 154]. Additionally, the optimal control model J_{CDI} contains little of the internal structure that is often necessary for monotonicity to arise. However, there are some conditions where a monotonic control function may be optimal. In this section we explore and characterize this regime for a compartmental model that is a simplified version of the one used in J_{CDI}. Figure 26 displays the simplified compartmental model governing CDI transmission.

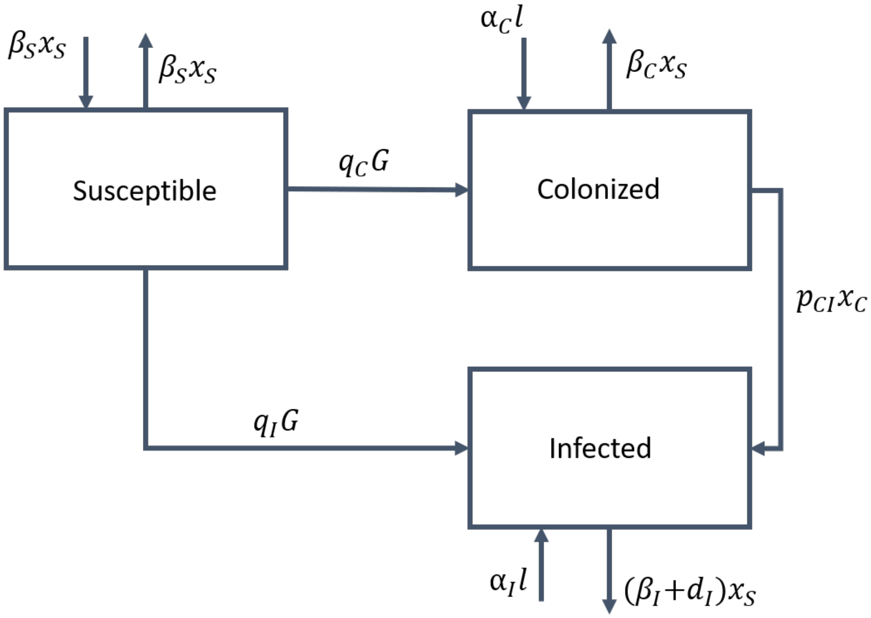


Figure 26: Simplified CDI compartmental model

For this simplified model, we limit our analysis to just a single control variable u. We express the optimal control problem associated with the compartmental model as follows,

$$\text{maximize}_{u,l} \quad \int_0^T \{-c_1 x_C - c_2 x_I\} dt \tag{J_{SCI}}$$

$$\text{subject to} \quad \dot{x}_S = \beta_S x_S - \beta_S x_S - (q_I + q_C G) \tag{A.1}$$

$$\dot{x}_C = \alpha_C l + \beta_C x_C + q_c G - p_{CI} x_C \tag{A.2}$$

$$\dot{x}_I = \alpha_I l + (\beta_I + d_I) x_I + p_{CI} x_C + q_I G \tag{A.3}$$

$$\dot{b} = -u \tag{A.4}$$

$$b(T) \geq 0 \tag{A.5}$$

$$b(0) = b^0 \tag{A.6}$$

$$x(0) = x^0 \tag{A.7}$$

$$0 \leq x_S + x_C + x_I \leq H \tag{A.8}$$

We also require a few assumptions on specific parameters in J_{SCI},

- G is decreasing and convex in u
- $G_C > G_S \geq 0$ and $G_I > G_S \geq 0$
- $c_2 > c_1 > 0$

Lemma A.4.1 (Maximum Principle)**.** *Let u^* be a piecewise continuous optimal control that solve the problem J_{SCI} with corresponding optimal trajectory x^*, b^*. Let y_i be the shadow price corresponding to the state constraint for x_i, and let z be the shadow price corresponding to the state constraint of b. Whenever x is an interior point (i.e., $0 < x_S + x_C + x_I < H$ and $b > 0$), then the following conditions must hold,*

1. $\dot{y}_S = G_S[y_s - y_C q_C - y_I q_I]$

2. $\dot{y}_C = c_1 + y_S G_C - y_C q_C G_C + y_c \beta_C + y_C p_{CI} - y_I q_I G_I - y_I p_{CI}$

3. $\dot{y}_I = c_2 + y_S G_I - y_C q_C G_I - y_I q_I G_I + y_I \beta_I$

4. $\dot{z} = 0$

5. $z(T)b(T) = 0$

6. $y_S(T) = y_C(T) = y_I(T) = 0$

7. y, z *are continuous*

8. $\mathcal{H}(u^*, x^*, y, z, t) \geq \mathcal{H}(u, x^*, y, z, t)$ *for all feasible* u *where* $\mathcal{H} = -c_1 x_C - c_2 x_I + y_S[\beta_S x_S - \beta_S x_S - (q_I + q_C G)] + y_C[\alpha_C l - \beta_C x_C + q_c G - p_{CI} x_C] + y_I[\alpha_I l + (-\beta_I - d_I) x_I + p_{CI} x_C + q_I G] - zu$

Proof. All the conditions follow directly from the Maximum Principle, as expressed in Theorem 2.3 in [166]. By assuming that x is an interior point, we may disregard the terms of pure state constraints (representing hospital capacity). This assumption is reasonable, as we have a daily, positive arrival rate l for which a strictly positive proportion of which are colonized or infected. We may define the Hamiltonian $\mathcal{H}$ as,

$$\begin{aligned}\mathcal{H} = &-c_1 x_C - c_2 x_I + y_S[\beta_S x_S - \beta_S x_S - (q_I + q_C G)] + y_C[\alpha_C l - \beta_C x_C + q_c G - p_{CI} x_C] \\ &+ y_I[\alpha_I l + (-\beta_I - d_I) x_I + p_{CI} x_C + q_I G] - zu\end{aligned}$$

Then to derive the expressions for the change in shadow prices,

$$\begin{aligned}
\dot{y}_S &= -\frac{\partial \mathcal{H}}{\partial x_S} = y_S G_S - y_C q_C G_S - y_I q_I G_S = G_S[y_s - y_C q_C - y_I q_I] \\
\dot{y}_C &= -\frac{\partial \mathcal{H}}{\partial x_C} = c_1 + y_S G_C - y_C q_C G_C + y_C \beta_C + y_C p_{CI} - y_I q_I G_C - y_I p_{CI} \\
\dot{y}_I &= -\frac{\partial \mathcal{H}}{\partial x_I} = c_2 + y_S G_I - y_C q_C G_I - y_I q_I G_I + y_I(\beta_I + d_I) \\
\dot{z} &= -\frac{\partial \mathcal{H}}{\partial b} = 0
\end{aligned}$$

□

From condition 8 and from Theorem 1 in Hartl, et al [167], we can develop the following additional condition, which must be satisfied by an optimal control u^* at nearly all t.

$$\begin{aligned}
\mathcal{H}_u &= \frac{\partial \mathcal{H}}{\partial u} \\
&= y_S[-(q_C + q_I)G_u] + y_C[q_c G_C] + y_I[q_I G_I] - z \\
&= G_u[-y_S + q_C y_C + q_I y_I] - z \\
&= G_u[q_C(y_C - y_S) + q_I(y_I - y_S)] - z = 0 \qquad \text{(A.9)}
\end{aligned}$$

We note that A.9 does not hold when $t = T$, because $\mathcal{W}(T) = q_C(y_C(T) - y_S(T)) + q_I(y_I(T) - y_S(T)) = 0$, while $z > 0$ for a sufficiently tight budget. However it is clear from the transversality conditions (5 and 6) that $u(T) = 0$ for a sufficiently tight budget,

We use A.9 to develop qualitative conditions under which the optimal control u^* displays monotonic properties.

Proposition A.4.1 (Monotonicity in time). *In any time interval* $[t_1, t_2]$ *where* $\dot{y}_C - \dot{y}_S \geq 0$ *and* $\dot{y}_I - \dot{y}_S \geq 0$*, then* $u^*(t)$ *must be non-increasing over* $[t_1, t_2]$.

Proof. We first remark on a few characteristics of the shadow prices y, z. First, we note that $z(t) \geq 0$. This must be the case, as an additional dollar available for infection control at any point in the planing period can only decrease the total infection-related cost. We also note that as the planning period budget becomes smaller (i.e., as b_0 decreases), z must increase. We also note that $z(t)$ must be a non-negative constant, as $\dot{z} = 0$. Finally, $y \leq 0$, as an additional patient of any type can become colonized/infected and contribute to the disease-related costs.

Then, condition A.9 can be written as,

$$G_u[q_C(y_C - y_S) + q_I(y_I - y_S)] = z$$

Because $G_u \leq 0$ and $z \geq 0$, it follows that $\mathcal{W} = [q_C(y_C - y_S) + q_I(y_I - y_S)] \leq 0$. Because z is a constant, G_u and $\mathcal{W}$ must 'balance' at each time step t.

Then, we further investigate the relationships of $\dot{y}_C - \dot{y}_S$ and $\dot{y}_I - \dot{y}_S$

$$\begin{aligned}\dot{y}_C - \dot{y}_S &= c_1 + y_S G_C - y_C q_C G_C + y_C \beta_C + y_C p_{CI} - y_I q_I G_C - y_I p_{CI} - y_S G_S \\ &\qquad + y_C q_C G_S + y_I q_I G_S \\ &= c_1 + (y_S - y_C q_C - y_I q_I)[G_C - G_S] + y_C \beta_C + p_{CI}(y_C - y_I)\end{aligned}$$

By assumption, $c_1 > 0$. Thus, for $\dot{y}_C - \dot{y}_S \geq 0$, it must be the case that $(y_S - y_C q_C - y_I q_I)[G_C - G_S] \geq -y_C \beta_C - p_{CI}(y_C - y_I)$. This term translates to conditions where the cost of another exposure is offset by the benefit of removing a colonized patient (whether from a discharge or from transitioning to infected). Similarly, we analyze,

$$\dot{y}_I - \dot{y}_S = c_2 + (y_S - y_C q_C - y_I q_I)[G_I - G_S] + (\beta_I + d_I) y_I$$

This again implies that $\dot{y}_I - \dot{y}_S \geq 0$ if the cost of another exposure is offset by the cost of removing an infected patient. If such conditions hold and $\dot{y}_I - \dot{y}_S, \dot{y}_C - \dot{y}_S \geq 0$, then to ensure the RHS of A.9 remains a positive constant, G_u must be non-increasing, which is only possible if u itself is non-increasing. □

A.4.2 Alternate linearization formulation

To solve the optimal control problem as a MIP, we use variables γ as linearizing multipliers. The constraints governing these multipliers is described in 5.15, 5.16, and 5.17. While these are correct in the sense that they enforce the desired relationship between γ, δ, and u, we note that there exists a more concise form of these constraints that theoretically produces a tighter relaxation of the MIP. These constraints are expressed as follows,

$$\sum_{v \in V} \gamma^t_{vw} = \delta^t_w, \quad \forall w \in W, t = 0, 1, ..., T \tag{A.10}$$

$$\sum_{w \in W} \gamma^t_{vw} = u^t_v, \quad \forall v \in V, t = 0, 1, ..., T. \tag{A.11}$$

A.4.3 Alternate objective function for MIP

We note that it may be desirable to minimize the number of hospital-associated CDIs, rather than some overall infection-related cost as in M. Such an objective function could be expressed as follows,

$$\begin{aligned} \text{maximize} \quad & \sum_{t \in T} -q_I \sum_{v \in V} \sum_{w \in W} \gamma^t_{vw} G(v, w) - p_{CI}[\sum_{w \in W} \delta^t_w w]_C \qquad (M') \\ \text{subject to} \quad & (5.10) - (5.23). \end{aligned}$$

The objective function of M' can potentially take on extremely small values, especially for high budgets. This would very likely lead to instances of the model that are very difficult to solve or reach a satisfactory optimality gap. However, it is possible to demonstrate that both M and M' achieve the same optimal policy, and we can therefore be assured that an optimal solution to M will also minimize our estimate of HA-CDIs.

Theorem A.4.1. *A policy u^*, l that is optimal for M will also be optimal for M'.*

Proof. We note that the feasible region for both these MIPs is the same, so any u^*, l^* optimal for M' will be feasible for M. We then just need to show that the objective function for M will be minimized if the objective function for M' is minimized under the same policy. Symbolically, for the same u, l,

$$min \sum_{t=1}^{m} x_C(t) + x_I(t) \implies min \sum_{t=1}^{m} q_I G(u, x) + p_{CI} x_C(t)$$

We prove this by induction on m. We let G^* represent the sequence of exposure rates optimal for M' under optimal u^*, l^* and corresponding x^*. Similarly, we let x, G be the state and exposure sequences optimal for M. We also assume that the initial conditions are the same for both MIPs.

We consider the base case where $m = 1$ (i.e., we are running M for a single decision period). We prove this case by contrapositive, by showing that if there exists a G^* that minimizes M', then $x_C + x_I$ cannot minimize M.

$$\begin{aligned}
\sum_{t=1}^{m} x_C(t) + x_I(t) &= x_C(1) + x_I(1) \\
&= \alpha_C l(0) + [x(0)P]_C - \beta_C x_C(0) + q_C G \\
&\quad + \alpha_I l(0) + [x(0)P]_I - \beta_I x_I(0) - d_I x_I(0) + q_I G \\
&= \alpha_C(\beta + d)x(0) + [x(0)P]_C - \beta_C x_C(0) + q_C G \\
&\quad + \alpha_I(\beta + d)x(0) + [x(0)P]_I - \beta_I x_I(0) - d_I x_I(0) + q_I G \\
&\geq \alpha_C(\beta + d)x(0) + [x(0)P]_C - \beta_C x_C(0) + q_C G^* \\
&\quad + \alpha_I(\beta + d)x(0) + [x(0)P]_I - \beta_I x_I(0) - d_I x_I(0) + q_I G^* \\
&= x_C^*(1) + x_I^*(1)
\end{aligned}$$

The second equality follows from the fact that the arrival rate l, though determined by the MIP, can be written in terms of x for the closed hospital population. Then, for the inductive step,

$$\begin{aligned}
\sum_{t=1}^{m+1} x_C(t) + x_I(t) &= \sum_{t=1}^{m} \{x_C(t) + x_I(t)\} + x_C(m+1) + x_I(m+1) \\
&\geq \sum_{t=1}^{m} \{x_C^*(t) + x_I^*(t)\} + x_C(m+1) + x_I(m+1) \\
&= \sum_{t=1}^{m} \{x_C^*(t) + x_I^*(t)\} + \alpha_C(\beta + d)x(m) + [x(m)P]_C - \beta_C x_C(m) \\
&+ q_C G(x(m)) + \alpha_I(\beta + d)x(m) + [x(m)P]_I - \beta_I x_I(m) - d_I x_I(m) \\
&+ q_I G(x(m)) \\
&\geq \sum_{t=1}^{m} \{x_C^*(t) + x_I^*(t)\} + \alpha_C(\beta + d)x(m) + [x(m)P]_C - \beta_C x_C(m) \\
&+ q_C G^*(x(m)) + \alpha_I(\beta + d)x(m) + [x(m)P]_I - \beta_I x_I(m) - d_I x_I(m) \\
&+ q_I G^*(x(m)) \\
&= \sum_{t=1}^{m+1} x_C^*(t) + x_I^*(t)
\end{aligned}$$

The final equality follows from the fact that $[x(m)P]_I$, $[x(m)P]_C$, $\beta_C x_C(m)$, $\beta_I x_I(m)$, $d_I x_I(m)$ are identical regardless of whether the M or M' optimal policy is used, as these are deterministic transitions that depend only on x. □

A.4.4 Generalized control limit formulation

The control limit formulation described in M_{CL} requires that any intervention in use at any point in the planning period must be in use at $t = 0$. We present a more generalized version of M_{CL}, that allows for each intervention to be 'started up' at most once.

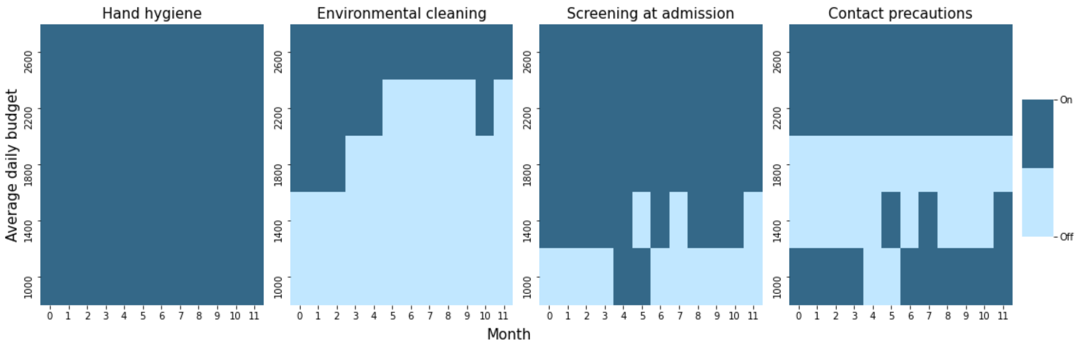
$$
\begin{aligned}
&\text{maximize}_u \quad \sum_{t\in\tau} -[\sum_{w\in W} \delta_w^t w]_C - [\sum_{w\in W} \delta_w^t w]_I && (M_{SCL})\\
&\text{subject to} \quad (5.10) - (5.23)\\
&\quad z_n^0 \geq |\sum_{v\in V} u_v^0 Y_{vn}|, \quad \forall n \in N\\
&\quad z_n^t \geq |\sum_{v\in V} u_v^t Y_{vn} - \sum_{v\in V} u_v^{t-1} Y_{vn}|, \quad \forall t = 1, ..., T, \forall n \in N\\
&\quad \sum_{t\in\tau} z_n^t \leq 2, \quad \forall n \in N\\
&\quad z_n^t \in \{0, 1\}, \quad \forall n \in N, t \in \tau.
\end{aligned}
$$

In M_{SCL}, we note that z_n^t is a status switch variable that will take on the value of 1 if the intervention n switches status between times t and $t-1$ (i.e., from 'on' to 'off' or from 'off' to 'on'). By the constraints included in this formulation, this status switch may happen at most twice, including any intervention startup when $t = 0$, resulting in the desired policy form.

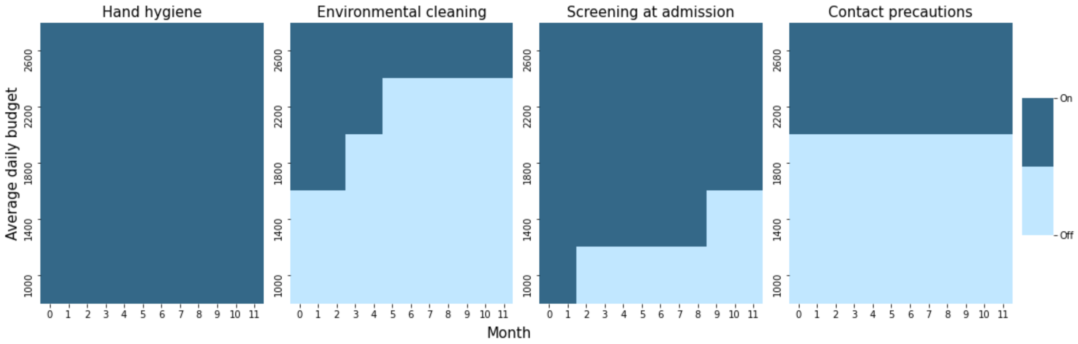
A.4.5 Baseline, including labor costs

Table 28: HA-CDI rate and total cost by policy and budget for baseline community hospital, including labor costs

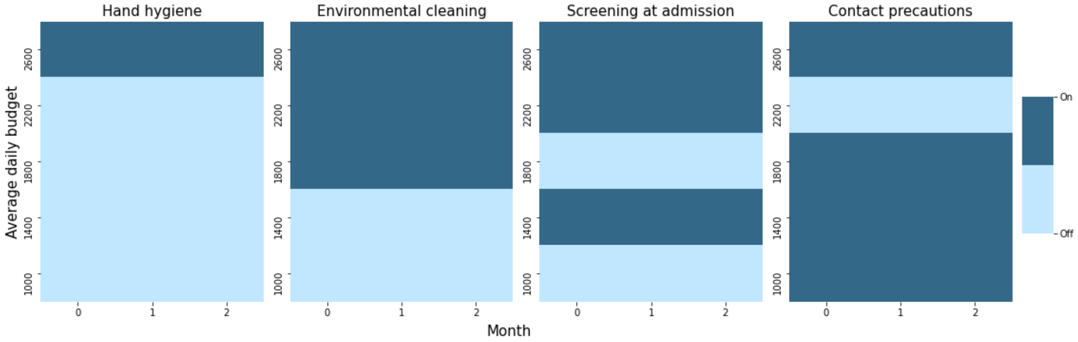
Average daily budget ($)	HA-CDI/10000 Patient Days					Total Costs		
	Dynamic	Control Limit	Static	D/CL Gap	CL/S Gap	Dynamic	Control Limit	Static
2600	2.00	2.00	2.00	0.0%	0.0%	865569	865569	865569
2200	2.23	2.24	2.78	0.4%	19.4%	713873	688647	742617
1800	2.47	2.47	2.71	-0.3%	8.9%	602034	602034	532059
1400	2.93	2.93	4.48	-0.1%	34.6%	472831	471191	479091
1000	4.88	5.14	6.45	5.0%	20.3%	338861	339965	227736



(a)



(b)



(c)

Figure 27: Optimal infection control policy under baseline case with labor costs, dynamic (a), control limit (b), and static (c)

A.4.6 Additional tables

Table 29: Comparison of MIP and Simulation estimates infection rate and total cost, dynamic policies

Average daily budget ($)	Simulated, HA-CDI rate	MIP, HA-CDI rate	Simulated, total cost	MIP, total cost
600	1.06	0.34	185818	211635
500	1.16	0.69	158226	179847
400	1.33	1.05	124427	143908
300	1.60	1.82	91154	105751
200	2.50	4.75	65916	71557
150	3.19	6.42	51550	52017

Table 30: MIP gap (solve time in seconds) by policy type,community hospital model, baseline scenario

Average daily budget ($)	Dynamic	Control Limit	Static
600	0.01% (408)	0.01% (408)	0.01% (27)
500	0.73% (43200)	0.14% (364)	0.41% (826)
400	1.42% (14400)	0.24% (1932)	0.00% (1006)
300	2.28% (28800)	0.00% (1562)	0.00% (1618)
200	3.78% (86400)	0.30% (2237)	0.00% (1640)
150	5.28% (14400)	0.27% (1646)	0.00% (6416)