The Role of Antimicrobial Stewardship in Modifying the Epidemiology of *Clostridioides difficile* Infection

by

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A dissertation submitted in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy
in
Epidemiology

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Oregon Health & Science University
2024

Abstract

Background: Clostridioides difficile infection (CDI) causes nearly half a million diarrheal illnesses annually in the United States and is associated with a twofold increase in the risk of death for hospitalized patients with CDI. Broad spectrum antibiotic therapy is a major risk factor for CDI. As such, healthcare-associated (HA) CDI is often employed as a metric to evaluate antimicrobial stewardship programs (ASPs). However, because the risk from antibiotics is heterogeneous and dependent on a variety of other individual and environmental risk factors, evidence that HA-CDI is a quality metric for stewardship success is lacking. The objective of this dissertation is to achieve a more granular understanding of the risk of HA-CDI from antibiotics, and to evaluate the specific contexts where we would expect HA-CDI incidence to reflect changes in broad spectrum prescribing through stewardship interventions.

Methods: In my first specific aim (Chapter 3), we performed a retrospective cohort study, using the antibiotic spectrum index (ASI) to granularly describe the risk of HA-CDI from antibiotic exposure after adjusting for various known CDI risk factors. We then translated our results into absolute risk differences and number needed to harm values (NNH) to describe risk attributable to broad spectrum antibiotic therapy. In my second specific aim (Chapter 4), we conducted an interrupted time series analysis examining HA-CDI risk factors and HA-CDI incidence before and during the first two years of the COVID-19 pandemic. In my third specific aim (Chapter 5), we constructed a stochastic mathematical model to simulate how ASPs alter HA-CDI incidence in a variety of hospital settings.

Results: In Aim 1, we demonstrated that ASI accurately describes HA-CDI risk after controlling for important confounders. ASI (per antibiotic day) also fit our data better than days of therapy (DOT), a more commonly used measure of antibiotic use. In Aim 2, we identified substantial increases in a number of HA-CDI risk factors including frequency and intensity of antibiotic prescribing, number of comorbid conditions, time at-risk, and average patient age following the start of the COVID-19 pandemic. However, despite the elevation of risk factors, we did not detect significant differences in HA-CDI rate. Finally, our Aim 3 model was able to simulate HA-CDI epidemiology in a large acute care hospital setting. Proportion of *C. difficile* colonized individuals, and high-risk antibiotic use prior to admission were highly influential in the model, as was the rate of *C. difficile* transmission in the hospital. HA-CDI proportionally declined after simulated stewardship initiatives in most contexts, with the exception of when the proportion of those receiving high-risk antibiotics prior to admission was greater than 20 percent.

Conclusions: This dissertation work highlights the importance of context when applying HA-CDI as a metric to evaluate ASP success. We demonstrated that ASI accurately describes HA-CDI risk from antibiotics in Aim 1. In Aim 2, we hypothesize that infection prevention measures limited the increase in HA-CDI incidence despite increases in other risk factors. And finally, our Aim 3 model incorporated this information allowing us to evaluate the specific hospital contexts where HA-CDI is a quality metric for stewardship success. We conclude that a regional focus on stewardship and a focus on pre-admission antibiotic use and *C. difficile* colonization are of vital importance and must be considered when using HA-CDI as a patient centered ASP outcome.

Acknowledgements

A dissertation is simultaneously a lonely process and a collaborative one. Despite long hours sitting alone at my computer, I could not have accomplished any of this without support from many wonderful people, both personal and professional. First, I would like to thank my advisor and committee chair Dr. Jessina McGregor for sharing her vast knowledge as an epidemiologist and for helping me navigate this PhD program as I became a new parent. I would also like to thank the rest of my dissertation committee, Dr. JJ Furuno, Dr. Luke Strnad, and Dr. Eric Lofgren. After hearing a few dissertation committee horror stories, I am grateful to my committee for being supportive, available, and above all else, genuinely nice people. I would like to thank my current and former OSU College of Pharmacy colleagues. Specifically, Caitlin McCraken for helping wrangle the massive amounts of data required for this dissertation, Dr. Kendall Tucker for providing clinical knowledge at a moment's notice, Olivia Arar for helping me communicate my results more clearly, and all three, for being lovely people.

Next, I would like to thank the OHSU-PSU School of Public Health and the PhD Epidemiology program. Dr. Lynn Mashall's leadership throughout my time in the program was incredibly valuable. I am a better scientist because of Dr. Marshall's standards. I am also incredibly grateful to my PhD cohort, Dr. Abigail Newby-Kew, Sarah Tran, and Jonah Geddes. It is impossible to describe the bonds forged throughout this process. These three have inspired me as scientists, parents, and all-around people.

I would like to thank my past mentors in Chicago, Dr. Bill Trick and Dr. Mike Lin. I was able to have some early-career success thanks to these two. I would not have entered a doctoral program without this experience.

Finally, I would like to thank my family. My parents, Rod and Chris, and my wife's parents, Liz and Conrad. This dissertation would have been impossible without their support. Last but certainly not least, I want to thank my wife, Beckah, and our two boys, Jonah and Declan. This process has been a whole family affair. Thank you three for your love and your undying patience. We did it! I'm a doctor (and I'll never not be a doctor)!

Table of Contents

List of Tables

Chapter 1: Introduction and Research Aims

Chapter 2: Review of the Literature

Chapter 3: Influence of Antibiotic Exposure Intensity on the Risk of *Clostridioides difficile* infection

List of Figures

Chapter 1: Introduction and Research Aims

Chapter 2: Review of the Literature

Chapter 3: Influence of Antibiotic Exposure Intensity on the Risk of *Clostridioides difficile* infection

Chapter 4: Examining the Impact of the COIVD-19 Pandemic on Hospital-associated *Clostridioides difficile* Infection

List of Abbreviations

ABC	Approximate Bayesian Computation
AIC	Akaike Information Criterion
ASI	Antibiotic Spectrum Index
ASP	Antimicrobial Stewardship Program
AUR	Antibiotic Use and Resistance
CA	Community-acquired
CARB	National Strategy for Combating Antibiotic Resistant Bacteria
CDC	Centers for Disease Control and Prevention
CDI	*Clostridioides difficile* Infection
CI	Confidence Interval
DDD	Defined Daily Doses
DOT	Days of Therapy
ED	Emergency Department
FMT	Fecal Microbiota Transplantation
GEE	Generalized Estimating Equations
GI	Gastrointestinal
H2RA	H2 Receptor Antagonists
HA	Hospital-associated
HAI	Healthcare-associated Infection
HCUP	Healthcare Cost and Utilization Project
ICD-10-CM	International Classification of Disease Clinical Modification 10th Revision
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
IP	Infection Prevention
IRR	Incidence Rate Ratio
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
NG	Nasogastric
NHSN	National Healthcare Safety Network
NNH	Number Needed to Harm
OHSU	Oregon Health & Science University
PCR	Polymerase Chain Reaction
PPE	Personal Protective Equipment
PPI	Proton Pump Inhibitors
QIC	Quasi-likelihood under Independence Model Criterion
RR	Relative Risk
SAAR	Standardized Antimicrobial Administration Ratio
SHEA	Society for Healthcare Epidemiology of America
SIR	Standardized Infection Ratio
UK	United Kingdom
US	United States

Chapter 1: Introduction and Research Aims

1.1 Introduction

Clostridioides difficile infection (CDI) causes nearly half a million illnesses annually in the US. Manifesting as severe diarrheal illness, CDI is associated with prolonged hospitalization and a 50-100% increase in mortality compared to hospitalized individuals without CDI [1]. One in five individuals will have a recurrence in the subsequent 2-8 weeks [2]. There is a delicate balance between effective, targeted antibiotic therapy and intense therapy that disrupts the normal gastrointestinal microbiota, creating opportunities for *C. difficile* to colonize an already compromised hospitalized individual. Since *C. difficile* spores can persist on surfaces for weeks, CDI can be transmitted person to person directly or via the environment, making the tandem of infection prevention (IP) strategies and antimicrobial stewardship programs (ASP), and specifically how these factors operate within the *overall context* of the healthcare environment (e.g. colonization pressure, demographics, IP activities), critically important factors in CDI epidemiology requiring further study.

As much as half of antibiotics prescribed in US hospitals and clinics are inappropriate or altogether unnecessary [3, 4]. In response, the US Government mandated the creation of ASPs in 2014 with the goal of optimizing patient outcomes while limiting the emergence and spread of antibiotic resistance [5]. Because CDI is strongly associated with the use of antibiotics, and because of a renewed focus on patient-centered outcomes, ASPs commonly use CDI rate as a metric for intervention

success. However, results in CDI reduction after a new stewardship intervention have been variable. In a recent meta-analysis, 5 of 11 evaluated programs did not show a significant reduction in CDI despite demonstrating reductions in antibiotic use [6]. ASPs, in general, and the related causal association between antibiotic therapy and CDI are challenging to assess. The CDI risk attributable to the individual varies widely by antibiotic type and duration of therapy, requiring a large study sample to assess agent-specific risks individually with any granularity. Furthermore, the complex constellation of causal factors associated with CDI mean that mitigating one risk factor (i.e. antibiotic use) is not always followed by a proportional decrease in CDI rate. Therefore, while using overall CDI rate as an indicator of ASP success is widespread, it is unclear if it is a relevant patient outcome in all settings. Additionally, the novel coronavirus disease (COVID-19) pandemic has significantly altered the healthcare context, with changing patient populations due to the temporary halting of elective procedures and the proliferation of video healthcare visits, a renewed focus on hand hygiene and environmental cleaning, and likely changes in antibiotic prescribing due to an increase in empiric prescribing and a decrease in prophylaxis for elective surgeries. This changing landscape not only necessitates an evaluation of the virus's impact on CDI due to the direct influence on IP measures and antibiotic prescribing, but also presents a unique opportunity to evaluate the relative importance of various contextual factors that drive CDI incidence.

1.2 Research Aims

The main goal of this project is to evaluate the set of conditions required to observe clinically meaningful reductions in CDI rate after ASP initiatives. This work could shift the current paradigm for evaluating ASP initiatives by illuminating the conditions in which ASP-driven reductions in CDI might be expected or when another metric might be needed. I propose to address this research question through the following specific aims:

Research Aim 1: Measure the association between intensity of antibiotic therapy, based on the antibiotic spectrum index, and CDI incidence, controlling for other factors that drive CDI rate beyond antibiotic use. The risk of CDI from antibiotics is heterogeneous and dependent on the intensity (i.e., spectrum and duration) of antibiotic therapy. Thus, the impact of stewardship interventions on CDI incidence is variable, and understanding this risk requires a more granular measure intensity of therapy than traditionally used measures like days of therapy (DOT). I performed a retrospective cohort study to measure the independent association between intensity of antibiotic therapy, as measured by the antibiotic spectrum index (ASI), and hospital-associated CDI (HA-CDI) at a large academic medical center.

Research Aim 2: Quantify the impact of changes to the hospitalized patient population and healthcare delivery due to the COVID-19 pandemic on the hospital level CDI rate. Though much is known about HA-CDI, the COVID-19 pandemic significantly altered the

healthcare context, providing an opportunity to study the virus's impact on CDI due to a direct influence on both modifiable and unmodifiable risk factors. I performed an interrupted time series analysis establishing March 23, 2020 as the primary interruption point (pandemic start), examining HA-CDI trends and trends in known CDI risk factors across 24 pre-pandemic and 24 pandemic-era 30-day time intervals.

Research Aim 3: Build and test a mathematical model that explains how hospital-level antimicrobial stewardship interventions impact CDI rates given variation in antibiotic use patterns and facility colonization pressure. I built stochastic, compartmental model to simulate ASP interventions in various healthcare contexts. This includes high in-hospital *C. difficile* transmission, higher proportions of colonized/infected individuals admitted to the facility, and varying rates of pre-admission high-risk antibiotic prescribing.

Chapter 2: Review of the Literature

2.1 Overview of *Clostridioides difficile* and *Clostridioides difficile* infection

2.1.1 Burden of disease – morbidity, mortality, recurrence, and cost

The *Clostridioides difficile* bacterium is responsible for 15% to 25% of all cases of antibiotic-associated diarrhea worldwide [7, 8]. A 2019 meta-analysis estimates a global healthcare-associated (defined below) *Clostridioides difficile* infection (CDI) incidence of 2.24 cases per 1000 admissions per year and 3.54 cases per 10,000 patient-days, with a high degree of heterogeneity mostly due to variation in surveillance definitions (range: 0 to 35.15 cases per 1000 admissions per year and 0.11 to 50.3 cases per 10,000 patient-days) [9]. A second meta-analysis estimates 8.3 cases per 10,000 patient-days, also with substantial variation (2.8 to 15.8 cases per 10,000 patient days) [10].

The annual estimated CDI burden in the United States CDI was nearly half a million incident infections in 2011, with an age- and sex-adjusted incidence rate of 147 cases per 100,000 people, approximately two thirds of which were healthcare associated [11]. The updated morbidity burden reported by the Centers for Disease Control and Prevention (CDC) in 2020 was 130 cases per 100,000 people. Local and national reduction strategies are thought to be responsible for much of this decrease in CDI incidence. However, the incidence of first recurrent infections and in-hospital deaths remains unchanged [12]. CDI is responsible for approximately 29,000 deaths in the United States annually [11, 12], and is considered an urgent public health threat by CDC [13]. Overall, approximately 1 in 6 CDI patients will have a recurrence, typically

defined as a new CDI infection 12 weeks after achieving a clinical cure for a previous CDI infection [14-17], though Infectious Disease Society of America/Society for Healthcare Epidemiology in America (IDSA/SHEA) guidelines define recurrence as a new infection within 2 to 8 weeks [18, 19]. There are an estimated 83,000 first recurrences of CDI in the United States yearly [11], and the recurrence rate has been relatively stable over the past decade despite an overall reduction in healthcare-associated CDI [12]. Estimates of asymptomatic *C. difficile* colonization upon hospital admission range from 3 to 21 percent [20-23]. CDI also places a substantial financial burden on the US healthcare system, with an estimated CDI-attributable cost of approximately $21,000 per case [24]. The total annual cost of CDI is thought to exceed $5 billion [25], and increases in hospital length of stay range from 2.8 to 16.1 additional days for CDI patients compared to non-CDI patients [26].

CDI is typically associated with either the healthcare or community setting, with different risk factors, populations, and strains of the organism associated with each [27]. Community-acquired CDI (CA-CDI) is defined as "Symptom onset in the community ≤72 hours after admission to a healthcare institution, provided that symptom onset was more than 8 weeks after the last discharge from a healthcare institution," and hospital-associated CDI (HA-CDI) is typically defined as symptom onset greater than 72 hours after admission [19, 28]. While there has been a decline in HA-CDI, the incidence of CA-CDI increased twofold over the past decade, perhaps representing a new and important at-risk population [27]. Much of the increased CDI incidence in the United States is attributable to the hypervirulent ribotype NAP1/BI/027 strain of *C. difficile,* which

appeared in the early 2000s. This strain produces larger amounts of toxins, which are associated with more severe symptoms and a higher likelihood of death and/or recurrence [29].

2.1.2 Bacterium specifics

C. difficile itself is a Gram-positive, anaerobic, spore-forming bacterium that was first isolated by Hall and O'Toole in 1935 [30, 31]. *C. difficile* produces an enterotoxin (Toxin A) and a cytotoxin (Toxin B) [23, 32], which cause *C. difficile*-associated diarrhea [31-33]. Toxin levels are generally correlated with the severity of illness [34, 35]. The disease progression is a multi-step process, where disruption of the colonic microbiome is followed by *C. difficile* (from either an endogenous or exogenous source) spore germination and colonization of the intestinal tract. As the cells multiply, they produce Toxin A and B, which precipitate the clinical symptoms of symptomatic CDI [35].

2.1.3 Signs, symptoms, and diagnosis

In addition to diarrhea (3 or more loose stools in 24 hours), abdominal pain, nausea, vomiting and fever are symptoms associated with CDI [8]. Severe sequalae (fulminant CDI) include severe dehydration, hypotension, bowel perforation, toxic megacolon, and bloodstream infections potentially leading to organ failure and death [31, 36]. CDC defines CDI as "a positive *C. difficile* toxin assay or a positive *C. difficile* molecular assay (e.g. PCR) of a stool specimen from a resident of the surveillance catchment area who is 1 year of age or older." CDC defines a *new* case as someone with "a *C. difficile*-positive stool specimen greater than 8 weeks after the last positive specimen [37]." Note that this definition is used for surveillance (e.g., for the National

Healthcare Safety Network [NHSN]) and does not incorporate the presence of symptoms. Improved molecular testing methods have possibly led to over-diagnosing CDI and, thus, artificially inflating reported rates by as much as 50 percent [38]. Misdiagnosing asymptomatic *C. difficile* colonization as CDI precedes unnecessary expenditures and treatments, leading to adverse events and possible antimicrobial resistance. Hence, best practices state that laboratory-based diagnosis should be accompanied by clinical signs and symptoms to support a CDI diagnosis [39]. It is, therefore, important to consider changes in diagnostic criteria, technology, and reporting protocols when interpreting incidence trends. Because CDI is relatively difficult to diagnose, an agreed upon set of diagnostic criteria has historically been controversial [40]. A recent study comparing real-time polymerase chain reaction (PCR), *C. difficile* toxin assay, and *C. difficile* culture as diagnostic tools for CDI reports sensitivities for the three methods of 87%, 49%, and 65% respectively using any diagnostic tool (PCR, toxin assay, or culture) *combined* with clinical symptoms for Gold Standard comparison, suggesting that PCR is the most efficient tool to aid in the diagnosis of CDI [41].

2.1.4 Treatment

Historically, metronidazole was the preferred treatment for non-severe CDI [28, 31]. However, metronidazole has a high absorption rate across intestinal walls, which makes it difficult to achieve the necessary concentrations to eliminate *C. difficile* in the gut [31]. Oral vancomycin has replaced metronidazole as the recommended CDI treatment (severe, complicated, or fulminant) [28, 31]. Fidaxomicin, approved in 2011,

has also shown strong efficacy for mild, severe, and recurrent CDI [23, 28], though the drug is costly and remains under-utilized [42]. Table 2.1 outlines CDI treatment best practices, according to IDSA/SHEA guidelines [19, 43]. Treatment regimens typically last 10 days, except in the case of more severe CDI cases [19, 44]. Note that treatment recommendations are by disease severity, yet methods for identifying disease severity are not clearly defined. Nevertheless, the IDSA/SHEA guidelines provide supportive clinical data to assist with treatment decisions. Adherence to treatment guidelines is associated with improved outcomes, including time to symptom resolution [19]. Recurrent CDI is treated with similar antibiotic regimens, until the third recurrence where fecal microbiota transplantation (FMT) is the preferred course of treatment [23, 45]. FMT is a procedure where donor bacteria from healthy donor stool is used to restore intestinal bacteria [46], and has been shown to be a safe and effective method to prevent further recurrence and reduce mortality [18, 47, 48]. Synthetic FMT products have also shown promise [49]. A few *C. difficile* strains have exhibited antibiotic resistance, though most remain susceptible to frontline CDI treatment options [50, 51].

2.1.5 HA-CDI prevention

Preventing hospital-associated CDI requires a combination of accurate diagnostic testing, antimicrobial stewardship, prevention of “horizontal transmission” through infection prevention processes such as hand hygiene/environmental cleaning and contact precautions, and reduction of other modifiable risk factors [52]. IDSA/SHEA guidelines stress the importance of terminal room cleaning with sporicidal agents [19]. Researchers have also promoted antimicrobial surface coating to reduce the

environmental bioburden of pathogens [53]. Contact-free methods such as ultraviolet light disinfection of rooms have also shown promise as an infection prevention tool [54, 55]. Infection prevention strategies play an important role in mitigating all healthcare associated infections, not exclusively CDI.

Importantly, CDI prevention strategies are generally bundled, so it can be difficult to evaluate the effectiveness of individual prevention activities [52]. Diagnostic stewardship is also crucial (i.e., only testing for *C. difficile* when appropriate) to avoiding CDI case misclassification [56].

C. difficile, when present and not toxigenic, can be part of the healthy gut microbiota, as its colonization is suppressed by other, more robust anaerobes [57, 58]. The prevalence of colonization varies significantly by age, with the highest proportion in infants and a general decrease with age [59]. Recurrent CDI is associated with a decrease in indigenous microbiota diversity [60]. Probiotics have been prescribed, with varying levels of effectiveness, to repair the microbiota flora and prevent CDI. Multi-strain probiotics tend to perform better, though evidence in the literature is still insufficient [61, 62]. Shedding of heat-resistant CDI spores into the environment is the main source of person-to-person transmission, and symptomatic CDI patients are the major source of CDI shedding and transmission in healthcare settings. Infection prevention strategies like isolation have not been historically recommended for asymptomatic *C. difficile* carriers [19, 20, 43]. However, limited evidence suggests that detecting and isolating asymptomatic carriers is effective in reducing the incidence of

hospital-acquired CDI [63]. The role that asymptomatic *C. difficile* carriers play in the transmission of CDI in healthcare settings is not sufficiently understood.

2.1.6 Hospital-associated, community-acquired CDI, and colonization pressure

A key factor in HA-CDI epidemiology is *colonization pressure*, defined as the proportion of individuals already infected with an organism in a particular geographic location (e.g., hospital facility or ward) over given time period [64]. Specifically, in the case of CDI, as the proportion of *C. difficile* colonized individuals increases, so does the risk of *exposure* to and acquisition of *C. difficile* in a previously uncolonized individual [65, 66]. Measuring and accounting for colonization pressure represents a quality method to adjust for disease burden when assessing other causal factors [64]. Major changes in colonization pressure could have a large impact on CDI transmission in the healthcare setting, and multiple studies report that colonization pressure is a strong independent risk factor for *C. difficile*-associated diarrhea and, therefore, should be accounted for when analyzing other CDI risk factors [67, 68].

2.2 Antibiotic-specific CDI risk

Receipt of broad-spectrum antibiotics is a primary individual-level risk factor for CDI [31, 69-72]. In the 2020 updated Antibiotic Resistance and Use (AUR) module, CDC lists the following as antibacterial agents that pose the greatest risk for CDI: cefdinir, cefepime, cefixime, cefotaxime, cefpodoxime, ceftazidime, ceftriaxone, ciprofloxacin, clindamycin, gemfloxacin, levofloxacin, and moxifloxacin [73]. A 2023 modeling study yields similar results [74]. A recent study evaluating antibiotic-specific CDI risks in

Ontario nursing homes reports that receiving any antibiotic was associated with 1.8 times greater risk of CDI (95% Confidence Interval (CI): 1.55 to 1.97) compared to no antibiotic. Clindamycin, moxifloxacin, and cefixime represent the greatest risk increase, with approximately a 4-fold increase conferred by each. Longer duration of therapy was also associated with greater CDI risk. A 14-day course was associated with 1.27 times the risk of CDI compared to a 7-day course (95%CI: 1.21 to 1.30), and 5-day course was associated with 0.91 times the risk of CDI compared to a 7-day course (95% CI: 0.90 to 0.93) [72], consistent with other studies [75]. A recent meta-analysis reports that cephalosporins and clindamycin confer the greatest risk of CDI [76]. This heterogeneity of risk across types and durations of antibiotic therapy is important to consider carefully when further evaluating CDI risk.

2.2.1 Antibiotic stewardship and CDI

As much as half of antibiotics prescribed in US hospitals and clinics are inappropriate or altogether unnecessary, contributing to a rise in antibiotic resistance and CDI incidence over the past decade. In response in 2014, the Obama Administration released the National Strategy for Combating Antibiotic Resistant Bacteria (CARB), which "identifies priorities and coordinates investments: to prevent, detect, and control outbreaks of resistant pathogens recognized by CDC as urgent or serious threats, including carbapenem-resistant *Enterobacteriaceae* (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), ceftriaxone-resistant *Neisseria gonorrhoeae*, and *Clostridium difficile*…" [77]. The Administration also, through Executive Order, established the Federal Task Force for CARB to implement the new national strategy.

One of the major actions taken was a mandate to create antimicrobial stewardship programs (ASP) with the goal of optimizing patient outcomes (e.g. minimizing hospital length of stay, mortality) while limiting the emergence and spread of antibiotic resistance [5, 78]. This governmental action was a major turning point in the push for broadened stewardship activities.

Several studies have shown the impact of antibiotic prescribing and stewardship on CDI. One such study demonstrates the contribution of ward-level antibiotic use to CDI, where a 10% increase in ward-level antibiotic use was associated with a 2.1 per 10,000 patient-day increase in CDI [79]. This makes a case for ward-level stewardship measures to decrease CDI incidence. Another study describes a reduction in CDI incidence in the UK that is attributable to a reduction in fluroquinolone use after national restrictions were implemented, concluding that antimicrobial stewardship should be a "central component" of CDI prevention. In the study, fluroquinolone and cephalosporin use were highly correlated with national CDI incidence ($r = 0.88$), but less correlated with national antibiotic use ($r = 0.59$). Fluoroquinolone-resistant *C. difficile* isolates also declined by nearly 80 percent [80]. Similar findings were reported in a quasi-experimental study, with a reduction in fluoroquinolone use by over 100 defined daily doses (DDD) per 1000 occupied bed-days per month, and 0.34 times the incidence rate of CDI (95% CI: 0.20 to 0.58) [81]. A meta-analysis examining the impact of ASPs on CDI reports that stewardship programs were associated with a 32% reduction in CDI across all included studies, though 5 of the 11 studies included not show a significant reduction in CDI. The authors suggest that stewardship alone is not always effective, and

that infection prevention components (e.g. hand hygiene) paired with ASPs are ideal [6]. Bundled approaches to stewardship are common and encouraged [82]. Another meta-analysis reports approximately a pooled 50% reduction in CDI following stewardship interventions [83]. ASPs have also been shown to significantly reduce antibiotic-associated costs [84]. It has been previously demonstrated no change in 30-day readmission rate after a stewardship intervention, suggesting that reduction in antibiotic use does not adversely affect the patients involved [85]. However, there remains some uncertainty in the literature around CDI as a metric for stewardship success [86].

2.3 Context-specific risk factors

2.3.1 Demographics and host-level risk factors

Comorbid conditions play an important role in CDI risk. Chronic kidney disease, diabetes, hematologic cancers, and inflammatory bowel disease have been proven to be associated with CDI [87, 88]. More generally, severity of underlying illness was shown to be associated with CDI [89]. The accumulation of comorbid conditions is associated with CDI incidence and mortality. One study reports 1.26 times the risk of getting CDI (95% CI: 1.19 to 1.32) with each additional comorbidity score point (Elixhauser Comorbidity Index) [90], and an additional 30-day mortality study by identified a 6% increase in CDI mortality per unit increase in comorbidity score (Cumulative Illness Rating Score) [91]. Age is one of the strongest risk factors for CDI, both in terms of overall CDI risk and risk of contracting more severe CDI strains, with individuals over 65 having 1.77 times the odds of having the BI/NAP1/027 strain compared to having a less severe strain (95% CI:

1.31 to 2.38) [88]. Over 80 percent of CDI deaths occur in individuals aged 65 years and older [2].

Prior CDI is a substantial risk factor for developing recurrent CDI [71]. Other independent risk factors include older age, taking antibiotics during follow-up, and renal insufficiency [92]. A recent prospective cohort study reported that treatment with metronidazole and diagnosis by enzyme immunoassay toxin were the most robust predictors of recurrent CDI, with a 3-fold and 2-fold increase in risk, respectively. Failed treatment with metronidazole and subsequent recurrence is the primary reason that oral vancomycin is now the recommended treatment [93].

2.3.2 Other pharmacological risk factors

Acid suppressing medications, such as proton-pump inhibitors and histamine 2 receptor antagonists, have been shown to be significantly associated with CDI and recurrent CDI, according to several meta-analyses [76, 87-89, 94-97]. For example, one meta-analysis reports 1.58 times the odds of those with CDI having taken a gastric acid suppressant (95% CI: 1.06 to 2.34) compared to those not taking these medications [87]. A recent study reports that, among patients with CDI, proton-pump inhibitors are associated with 1.84 times the risk of recurrent CDI compared to those not taking proton-pump inhibitors (95% CI: 1.18 to 2.85) [98]. Gastric acid acts as a barrier to bacterial overgrowth in the gut, hence, acid suppression can disrupt the internal homeostasis and can lead to a proliferation of *C. difficile* spores [99]. Other non-antibiotic medications that have been shown to increase CDI risk include corticosteroids

(adjusted Odds Ratio (aOR) = 1.65, 95% CI: 1.14 to 2.38) [87, 100], and some non-selective non-steroidal anti-inflammatory drugs (NSAIDs) (aOR = 1.41, 1.06-1.87) [101].

2.3.3 Clinical and environmental risk factors

Factors such as nasogastric tube feeding and other gastrointestinal procedures have been identified as CDI risk factors [71, 88, 89], with one study reporting that those with CDI had 3.6 times the odds of exposure to nasogastric tube feeding (95% CI: 1.0 to 14.3) [102]. Prior hospitalization is a major risk factor for CDI, with a reported 4% increase in the risk of CDI for each additional hospital day [102]. An estimated 50 percent of previously *C. difficile* uncolonized patients became colonized after staying in the hospital for more than four weeks, with the duration ranging from 12 to 71 days until colonization [20, 103, 104]. There is nearly a 20-fold increase in odds of CDI if the individual was in the emergency department [105]. The difference in hospital length of stay between CDI and non-CDI patients ranges from 3 to 21 days [10]. Nursing home residence is also a major predictor for CDI, mostly due to advanced age, immunosuppression, comorbid conditions, pharmaceutical interventions, and increased risk of infection due to proximity to other potentially colonized individuals [106, 107]. Nearly a quarter of CDI cases in the United States have symptom onset in nursing homes [11].

2.4 SARS-CoV-2 and CDI

2.4.1 COVID-19 and its impact on the healthcare system

In February of 2020, SARS-CoV-2, which causes COVID-19 disease, had been reported in 26 countries, including the United States [108]. The first presumptive case was detected in Oregon on February 28, 2020 [109]. The World Health Organization declared the pandemic on March 11, 2020, dramatically altering the daily lives of the majority of the planet and spurring a major shift in healthcare practice and delivery [110]. Table 2.2 outlines other key pandemic dates.

In March of 2020, Oregon Governor Kate Brown issued an executive order that, among other actions, put a moratorium on elective and non-urgent procedures for approximately three months. The primary reason for this was to conserve personal protective equipment (PPE), as PPE shortages were among the greatest concerns during the early part of the pandemic [111]. Restrictions on hospital and long-term care visitation were also implemented at this time. This response to the pandemic altered the population of hospitalized patients and placed a heightened awareness of handwashing, environmental cleaning, and infection prevention measures, impacting CDI and other healthcare-associated infections [112, 113]. A US-based multi-center cohort study reported a nearly 150 percent decrease in number of hospitalized patients between April and June of 2020, though with a 40 percent increase in ICU admissions [114]. A US Healthcare Cost and Utilization Project (HCUP) analysis reported a 20 percent decrease in urban-area hospital admissions in June – April 2020 compared to the same time the year prior. All-cause in-hospital deaths increased by 47 percent during the same period, with 1 in 10 hospitalizations and 1 in 3 in-hospital deaths among patients 65 years and older being COVID-19-related [115]. Patient-reported

experiences of care also declined throughout the pandemic [116], and a national survey of clinicians reports frequent staffing shortages, repurposing of non-ICU beds to ICU beds, and overall substandard care for non-COVID-19 patients compared to COVID-19 patients [117].

2.4.2 Changes in antibiotic prescribing during the pandemic

During the COVID-19 pandemic, there were documented shifts in antibiotic utilization for suspected COVID-19 cases. Overall antibiotic use in hospitals increased early in the pandemic, with a 5 percent increase in overall antibiotic prescribing and a 22 percent increase in ceftriaxone compared to the same time in 2019. Prescribing then leveled off, though use remained high as the pandemic progressed [118]. Among confirmed COVID-19 patients, empiric treatment using broad-spectrum agents was initially common due to concerns for bacterial superinfection [119, 120], likely influenced by similar practice patterns for patients admitted with community-acquired pneumonia [121]. Additionally, over the course of the pandemic, different treatment options, including antibiotics, were explored in an attempt to mitigate COVID-19's high mortality rate [120]. A system-wide study conducted in the UK reports an overall decrease in antibiotic prescribing at the onset of the pandemic, but an *increase* in prescribing by patient-day of care [122]. Investigators in a multi-center study conducted in South Carolina reported a 6.6 percent increase in overall antibiotic use and a 16.4 percent increase in antimicrobial agents primarily used to treat healthcare-associated infections (HAIs) [123]. The evidence is mixed as to whether remote medical consultations has resulted in an increase in antibiotic prescribing, with a systematic

review reporting mixed results when evaluating antibiotic prescribing over video healthcare visits after the pandemic's onset (4 studies reporting higher, 5 lower, and 3 similar prescribing rates) [124]. At the pandemic's onset, there was significant concern in the healthcare community that the COVID-19 pandemic will have a negative impact on antibiotic stewardship efforts due to factors like the redirecting of resources, staffing changes, surges in patient volume, and diagnostic uncertainty [125, 126].

2.4.3 The COVID-19 pandemic and CDI

A study conducted in Spain reports an increase in antibiotic use by about 10 defined daily doses per 100 bed-days compared to the pre-COVID period, and an approximately 70 percent decrease in healthcare-associated CDI. This suggests that heightened infection control procedures during the pandemic had a major impact on CDI reduction [127]. A single-center retrospective cohort study conducted in the UK reports a decrease in both CA- and HA-CDI from the pandemic's onset through June 2021, compared to the pre-pandemic period. The authors also reported a decrease in DDD of antimicrobials [128]. Another cohort study conducted in New York City reported no statistical differences in the HA-CDI standardized infection ratio (SIR) for 2020 compared to 2019 despite a clear uptick in antimicrobial prescribing during the pandemic period [129]. In a large study of 148 US hospitals, there was a significant association between COVID-19 burden and some healthcare-associated infections (central line-associated bloodstream infection, catheter-associated urinary tract infections, and MRSA bacteremia). However, HA-CDI was not associated with COVID-19 burden [130]. A study conducted in Ireland reported a decrease in HA-CDI [131]. A study

in Belgium reports a nearly 50 percent decrease in HA-CDI rate with no change in antibiotic prescribing. The authors hypothesize that the infection control measures could be responsible for the decrease, though they did not discount underdiagnosis due to a lack of *C. difficile* testing [132]. The overarching narrative in the literature is still uncertainty [133].

2.5 Mathematical modeling of CDI

Mathematical models are well suited to answering research questions regarding the interplay of multiple causal pathways that cannot be experimentally manipulated in practice. Studies evaluating the impact of ASP interventions on CDI rates are most commonly performed within a single center or hospital system and may be underpowered to detect significant changes. Additionally, infection prevention practices, community-onset CDI rates, and other factors are typically not considered in the analysis of the ASP intervention. Based upon the current understanding of the causal processes that influence hospital rates of CDI, it is likely that effects may only be observed when prescribing of high-risk antibiotics is reduced to a particular magnitude or for a sustained period of time [83]. Hence, a stochastic simulated environment provides the opportunity to experimentally manipulate these variables and identify scenarios under which ASP strategies may feasibly expect to impact CDI rates. A mathematical model will also allow us to consider the multifactorial risk for CDI in a simulated, controlled environment.

The current body of literature around *C. difficile*/CDI and mathematical modeling shows a great deal of variability in terms of model purpose, structure, and interventions evaluated. Agnew et al. describe CDI incidence across European countries and conclude that *C. difficile* transmission dynamics are largely influenced by each national context [134]. McLure et al. have published several models. One examines seasonal trends in CDI incidence, the conclusion being that seasonal variation in antibiotic prescribing tracks closely with that of CDI [135]. Another McLure group model aims to describe diverse sources of *C. difficile*, including animals, infants, and asymptomatically colonized adults. The authors report that transmission could plausibly be sustained by infants and asymptomatic carriers, rendering other interventions ineffective [136]. Other models simulate isolation of CDI/*C. difficile* colonized patients, suggesting this could be an effective means to curbing transmission [137, 138]. Two groups have used mathematical models to describe the utility of a potential toxoid vaccine against *C. difficile*, concluding that a vaccine would be effective only if there was a targeted vaccination strategy, interaction between hospitals and other vulnerable populations, and stress the importance of CDI cases being imported from outside the hospital [139, 140]. Lofgren and colleagues have studied the interaction between *C. difficile* and being in the ICU, concluding that this patient population is in need of particular attention due to increased mortality and hospital lengths of stay [141]. Lofgren et al. have also published a model examining the effectiveness of routine fecal microbiota transplantation in reducing CDI incidence and recurrence, noting promising results [142]. Lanzas et al. suggest through modeling that testing for *C. difficile* on admission to the hospital would

reduce new colonization and HA-CDI incidence [143]. Chamchod et al. report that infection control strategies are no longer effective in high CA-CDI and high colonization contexts [144]. Finally, Yakob et al. developed one of the only model that explicitly accounts for high-risk antibiotic prescribing, though the primary focus of the model was to examine the importance of imported CDI cases [145]. Summarizing this body of literature is systematic review by Gingras et al., concluding variability in published models makes results synthesis difficult, noting a need to focus on model calibration, structural uncertainties, and transparent reporting [146]. Focus has generally been on disentangling bundled interventions, and an overarching narrative emerges that external *C. difficile* sources and asymptomatic carriers are of vital importance. This suggests that additional modeling studies are needed to meaningfully inform CDI risk reduction efforts, including those specifically addressing ASP interventions.

Table 2.1. SHEA/IDSA recommendations for the treatment of *Clostridioides difficile* infection in adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment
Initial episode, non-severe	Leukocytosis with a white blood cell count of <15,000 cells/mL and a serum creatinine level of <1.5 mg/dL	• 10 days oral vancomycin OR • 10 days fidaxomicin • 10 days metronidazole if above agents unavailable
Initial episode, severe	Leukocytosis with a white blood cell count of ≥15,000 cells/mL and a serum creatinine level of ≥1.5 mg/dL	• 10 days oral vancomycin OR • 10 days fidaxomicin
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• Vancomycin by mouth or nasogastric tube • IV metronidazole with oral or rectal vancomycin esp. if ileus present
First recurrence	Recurrence definition: An episode of symptom onset and positive assay result following an episode with positive assay result in the previous 2–8 weeks	• 10 days oral vancomycin if metronidazole was use for initial treatment, OR • Prolonged tapered and pulsed vancomycin course if standard regimen was used for initial episode, OR • 10 days fidaxomicin if vancomycin was used for initial episode
Second or subsequent recurrence		• Tapered, pulsed vancomycin regimen, OR • 10 days vancomycin followed by 20 days rifaximin, OR • 10 days fidaxomicin, OR • Fecal microbiota transplantation

Sources [19, 43]

Table 2.2. Key OHSU timepoints for COVID-19 pandemic

Date	Event
January 19, 2020 [147]	First case of COVID-19 in the United States
*February 28, 2020 [109]	First presumptive COVID-19 case announced in Oregon
March 11, 2020 [110]	Pandemic declared by World Health Organization
March 23, 2020 [111]	Oregon Governor executive order 20-10 prohibiting elective and non-urgent procedures, non-essential visitation
June 15, 2020 [111]	Elective and non-urgent procedures resumed at OHSU
November 13, 2020 [148]	Two-week “freeze” due to increase in cases, hospital visitation limited
December 18, 2020	First vaccines arrive at OHSU
June 1, 2021	Start of delta wave
December 20, 2021	Start of omicron wave

*Patient first showed symptoms February 19, 2020

Chapter 3: Influence of antibiotic exposure intensity on the risk of *Clostridioides difficile* infection

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3.1 Abstract

3.1.1 Background

Antibiotics are a strong risk factor for *Clostridioides difficile* infection (CDI), and CDI incidence is often measured as an important outcome metric for antimicrobial stewardship interventions aiming to reduce antibiotic use. However, risk of CDI from antibiotics varies by agent and dependent on the intensity (i.e., spectrum and duration) of antibiotic therapy. Thus, the impact of stewardship interventions on CDI incidence is variable, and understanding this risk requires a more granular measure of intensity of therapy than traditionally used measures like days of therapy (DOT).

3.1.2 Methods

We performed a retrospective cohort study to measure the independent association between intensity of antibiotic therapy, as measured by the antibiotic spectrum index (ASI), and hospital-associated CDI (HA-CDI) at a large academic medical center between January 2018 and March 2020. We constructed a marginal Poisson regression model to generate adjusted relative risks for a unit increase in ASI per antibiotic day.

3.1.3 Results

We included 35,457 inpatient encounters in our cohort. Sixty-eight percent of patients received at least one antibiotic. We identified 128 HA-CDI cases, which corresponds to an incidence rate of 4.1 cases per 10,000 patient-days. After adjusting for known confounders, each additional unit increase in ASI per antibiotic day is associated with 1.09 times the risk of HA-CDI (Relative Risk = 1.09, 95% Confidence Interval: 1.06 to 1.13).

3.1.4 Conclusions

ASI was strongly associated with HA-CDI and could be a useful tool in evaluating the impact of antibiotic stewardship on HA-CDI rates, providing more granular information than the more commonly used days of therapy.

3.2 Introduction

Clostridioides difficile infection (CDI) causes nearly half a million diarrheal illnesses annually in the United States [1], and severe sequalae can include bowel perforation, toxic megacolon, bloodstream infections, and nearly a twofold increase in the risk of death for all hospitalized patients with CDI compared to those without [31, 36]. Despite effective treatment, one in five individuals will have a recurrence in 2-8 weeks [2]. Hospital-associated *C. difficile* infection (HA-CDI) is a major source of global morbidity, with an estimated 2.24 cases per 1000 hospital admissions each year [9]. CDI prevention requires a multi-faceted approach, but efforts to reduce broad-spectrum antibiotic exposures through antimicrobial stewardship play an important role [6, 71, 72, 79, 149].

CDI incidence is an important outcome often evaluated following antimicrobial stewardship program (ASP) interventions due to the high risk of CDI attributed to broad spectrum antibiotic therapy and the focus of ASPs on reducing excess broad-spectrum antibiotic use. Because the risk of CDI conferred by antibiotics varies by agent, with fluoroquinolones, clindamycin, and later-generation cephalosporins associated with higher levels of risk [73], traditionally used measures of antibiotic use, such as days of therapy (DOT), fail to capture complete information about the intensity of antibiotic therapy (i.e. the overall spectrum of activity for antibiotics or combinations of antibiotics over time). As an alternate tool to evaluate antibiotic stewardship, Gerber at al. developed the antibiotic spectrum index (ASI) to as a measure of antibiotic exposure weighted by spectrum of activity [150]. ASI was developed by surveying a panel of

experts on the coverage that individual antibiotics provide against a specified list of clinically important pathogens in the hospital setting. While ASI has previously been applied to other clinical outcomes [151], it has not been applied specifically to CDI.

To better support ASP intervention evaluations, we performed a retrospective cohort study to measure the independent association between intensity of antibiotic therapy, as measured by the ASI, and hospital-associated CDI (HA-CDI). We hypothesized that HA-CDI would be strongly associated with increasing ASI, and that ASI would more accurately predict HA-CDI risk compared to the more commonly used days of therapy (DOT).

3.3 Methods

3.3.1 Study Design and Data Source

We established a retrospective cohort of inpatients admitted to Oregon Health & Science University (OHSU) Hospital between February 25, 2018 and March 23, 2020. OHSU Hospital is a 576-bed academic medical center in Portland, Oregon. We established our study cohort as adult inpatients at risk for HA-CDI. The study cohort was limited to persons 18 years and older and excluded those with known recurrent or community-onset CDI, and those with hospital stays of less than four calendar days, as these individuals are not eligible to be diagnosed with HA-CDI (Figure 1). Excluded patients were still eligible to contribute to *C. difficile* colonization pressure (defined below). To detect instances of recurrent CDI, we reviewed data from 8-weeks prior to

the index admission at OHSU. We collected data on demographics, diagnoses, and medications from the Pharmacy Research Repository, a longitudinal repository of patient healthcare data developed in partnership with the OHSU Research Data Warehouse and supported by the Oregon Clinical and Translational Science Institute. These data have been validated and used in previous epidemiologic studies of medication utilization and treatment outcomes [152].

3.3.2 Hospital-Associated CDI

Our primary outcome was incident, non-recurrent HA-CDI, which we identified using a combination of medication administration and laboratory testing data (Box 1). Consistent with US Centers for Disease Control and Prevention HA-CDI definitions, we considered incident CDI to be hospital-associated if the date of first anti-*C. difficile* antibiotic administration or stool specimen sample collection from the positive *C. difficile* laboratory test (stool toxin assay or molecular PCR) fell on hospital day 4 or later. We considered CDI non-recurrent if no prior CDI events were identified at the index facility in the 8 weeks before the index CDI diagnosis date. We also performed a validation study of our case definition through comprehensive chart review and determined that our algorithm detected HA-CDI with 94% sensitivity (95% confidence interval: 87-98), 100% specificity (96-100), and 97% overall accuracy (93-99) [153].

3.3.3 Antibiotic Spectrum Index and Days of Therapy

Our primary exposure variable was antibiotic spectrum index (ASI) per antibiotic day, which was developed by Gerber et al. and represents the intensity of antibiotic

therapy in our study [150]. For antibiotic agents that were not evaluated in the original development of the ASI, we applied the same criteria to assign a spectrum index after consulting the literature and infectious disease pharmacists and physician coauthors (KJT, HP, and LCS). We aggregated a patient's ASI by summing ASI scores for each individual agent across all days of therapy or until the specimen collection date associated with an HA-CDI diagnosis. Finally, we divided the total ASI for a single hospital encounter by the patient's total number of antibiotic days to create our primary exposure variable. We also calculated DOT, which was defined as receipt of a singular systemic antibiotic agent on a calendar day, independent of the number of doses or the amount of antibiotic given [73, 154]. We summed all DOT for each patient's encounter. A single *antibiotic day* was any calendar day that a patient received at least one DOT.

3.3.4 Time at-risk and Colonization Pressure

A patient in our cohort was considered at risk for HA-CDI for the entire hospitalization or until a CDI diagnosis. We defined colonization pressure as the total daily number of individuals with CDI or a *C. difficile* positive laboratory test present on the ward during each patient's time at risk. Any patient in our overall patient population (including those excluded from our study cohort) was eligible to contribute to colonization pressure for the 14 days after initiation of first CDI treatment/positive test or until hospital discharge. We summed the daily number of CDI and/or *C. difficile* test-positive patients by hospital ward for every day a patient was present on the ward, which we defined as *case-days* of colonization pressure, an independent risk factor for

HA-CDI [64, 68]. We then divided case-days by days at risk to calculate average colonization pressure per patient-day at risk.

3.3.5 Additional Covariates/Potential Confounders

We evaluated several other potential confounders for inclusion in our final model. These include, during the current/index encounter, demographic factors (age, sex, race, ethnicity), pharmacological risk factors (proton pump inhibitors, H2-receptor antagonists, corticosteroids, non-steroidal anti-inflammatory drugs), and clinical risk factors (nasogastric tube placement, gastrointestinal procedures, chemotherapy, previous hospitalizations). We also calculated the Elixhauser comorbidity index, which categorizes patient comorbidities based on ICD-10-CM codes.

3.3.6 Statistical Analysis

We performed univariable analysis on each study variable to explore distributions and identify any missing data or potential outliers. We then examined bivariable associations between our primary exposure, outcome, and covariates to confirm variable relationships in our conceptual model (Appendix Figure 1). For bivariable comparisons, we used the Pearson chi-square test to test for differences between categorical variables and the two-sample t-test or Kruskal-Wallis test for differences between continuous variables.

We utilized a multivariable Poisson regression model to evaluate the independent association between antibiotic intensity (ASI per antibiotic day) and risk of CDI. We modeled our CDI outcome as binary, and the primary predictor (ASI per

antibiotic day) as continuous. To account for clustering due to multiple visits by the same patient, we used a generalized estimated equations approach (GEE), building a marginal model with robust covariance estimation to generate relative risks. To describe average differences in risk, we calculated adjusted predictive margins by varying ASI per antibiotic day values corresponding to common antibiotic regimens as well as the average marginal effect of ASI per antibiotic day on HA-CDI. We also calculated number needed to harm values and 95% confidence intervals to provide clinical applicability to our findings. To ensure adequate control for confounding, we utilized the "disjunctive cause criterion" proposed by VanderWeele, which recommends controlling for all covariates that cause the exposure or outcome regardless of statistical significance [155]. Based on empirical evidence, the following confounders were included in our full regression model *a priori*: time at-risk , age [2, 88], sum of Elixhauser comorbidities [87, 88, 90], days hospitalized in the previous 8 weeks [20, 103], inpatient antibiotic use in the previous 8 weeks , proton pump inhibitor or H2-receptor antagonist use [87, 88, 92], nasogastric tube placement [71, 88], other gastrointestinal procedures [71], corticosteroid use [87], chemotherapy [2, 156], source of hospital admission (Emergency Department, other healthcare facility, non-healthcare) [11], and *C. difficile* colonization pressure [67, 68]. All data management and statistical analyses were performed using SAS v.9.4.

3.4 Results

There were 75,056 inpatient encounters over the 2-year study period. After applying our exclusion criteria, 35,429 (47%) inpatient encounters remained to form our study cohort. Of our overall population cohort, 20% were under 18 years old, 44% had hospitalizations of less than 4 days, and 425 (0.5%) had either community-acquired or known recurrent CDI and were thus excluded (see Figure 1).

The cumulative incidence of HA-CDI in the study cohort was 0.36% or 4.1 cases per 10,000 patient-days. The median number of hospital days to HA-CDI diagnosis was 10 (interquartile range [IQR] = 7-16) days. Sixty-eight percent of our study population received at least one antibiotic during their hospitalization, with a median of 2 days of therapy (IQR = 0-7) and approximately 4.4 ASI units per antibiotic day (Table 1). Cephalosporins were the most commonly administered antibiotic class (59%) followed by penicillins (19%), macrolides (7%), and fluroquinolones (4%). The most common antibiotic agents administered were cefazolin (35%), ceftriaxone (9.5%), and cefepime (7.8%). Detailed antibiotic use is summarized in Appendix Table 1 and Appendix Table 2. Study patients were at risk for HA-CDI for a median of 6 days (IQR = 5-9) and had a median of 2 comorbidities (IQR = 1-3). Fifty-seven percent of our study sample received a proton pump inhibitor or H2 receptor antagonist during their hospitalization and 9% had a nasogastric tube placed. Study patients experienced a median of 1 case-day of *C. difficile* colonization pressure (IQR = 0-5) (Table 1).

There were no significant differences between patients with HA-CDI and patients without CDI by sex, age, race, or ethnicity (Table 1). Of the 128 patients with HA-CDI, 119 (93%) received at least one antibiotic during the encounter (excluding CDI

treatment drugs), compared to 68% of patients without CDI. Antibiotic therapy for patients with HA-CDI showed both longer median durations of therapy (8 vs 2 DOT) and broader spectrum/more intense therapy (mean ASI per antibiotic day 6.9 vs 4.4) compared to those without CDI. The HA-CDI group experienced 10-fold greater colonization pressure, both by total case-days (10 vs 1) and case-days per hospital day (1.0 vs 0.1) compared to those without CDI.

According to our fully adjusted model, each additional unit increase in ASI per antibiotic day was associated with 1.09 times the risk of HA-CDI (Relative Risk [RR] = 1.09, 95% Confidence Interval [CI]: 1.06-1.13) (Table 2). A 5-unit increase, which is the equivalent of receiving vancomycin or ceftriaxone per antibiotic day, was associated with a 1.55 times increased risk of HA-CDI compared to no antibiotic (RR = 1.55, 95% CI: 1.31-1.84). Relative risks for the other key risk factors in our model are summarized in Table 2.

The estimated baseline HA-CDI risk was 0.2% (95% CI: 0.14-0.26) according to our fully adjusted model. Each additional ASI point per antibiotic day is associated with a 0.03% change in absolute risk on average (risk difference = 0.03%, 0.02-0.04). We provide examples of the CDI risk conferred by frequently used antibiotics, adjusted risk differences, number needed to harm (NNH) values, and adjusted relative risks in Appendix Table 3. From our set of example antibiotic courses, NNH values ranged from 899 (95% CI: 690-1287) for the difference between vancomycin (or any ASI=5 antibiotic) and no antibiotics, and 232 (160-422), for the difference between a vancomycin/piperacillin-tazobactam combination (13 ASI) and no antibiotics. The NNH

for piperacillin-tazobactam, a well-known, high-risk agent for CDI that was administered to more than 2,700 patients during our study period, was estimated as 425 (325-611). This means that eliminating 425 courses of piperacillin-tazobactam from our average patient population would theoretically prevent one occurrence of HA-CDI. We also provide examples of NNH values for antibiotic de-escalation and mono vs combination therapy (Appendix Table 4). Compared to a 7-day course of piperacillin-tazobactam, de-escalating 1057 patients on hospital day 3 from piperacillin-tazobactam to ceftriaxone would prevent one HA-CDI case (NNH = 1057, 747-1808), as would de-escalating 578 patients from meropenem to ceftazidime on day 3 (NNH = 578, 398-1053). Treating 633 patients with azithromycin instead of a ceftriaxone-azithromycin combinations for 5 days would also theoretically prevent one HA-CDI occurrence (NNH = 633, 445-1086).

3.5 Discussion

ASI was strongly associated with HA-CDI. After adjusting for known confounders, each additional unit of ASI per antibiotic day was associated with approximately a 10 percent increase in HA-CDI risk on a relative scale, and 0.03% change on an absolute scale. Our results illustrate the utility of ASI in quantifying the risk of HA-CDI at the population level. Attributable risk and number needed to harm values also provide tools for estimating CDI reduction following stewardship interventions.

While observed absolute changes in risk were small, and thus, NNH values large, reduction in HA-CDI is still meaningful given the high frequency of antibiotic therapy

among hospitalized patients and associated morbidity and mortality caused by CDI. For example, more than 2,700 courses of piperacillin-tazobactam (NNH = 486) were administered during our study period. Additionally, due to the importance of colonization pressure, prevention of a single CDI case is important in the healthcare environment as *C. difficile* is transmitted via person-to-person or environmental contact [2]. We found that each additional case-day of colonization pressure doubles the risk of HA-CDI, controlling for other known risk factors. This is consistent with the literature stating that colonization pressure significantly impacts CDI epidemiology, independently from inpatient antibiotic use [64, 66, 68]. Finally, a single additional HA-CDI case could also have a significant impact on the CDC Standardized Infection Ratio (SIR), especially in low HA-CDI incidence environments (e.g. only a few HA-CDI cases per month), which could have implications in HA-CDI tracking and planning of interventions [157].

We also established that ASI provides information beyond DOT. If we utilize the same fully adjusted model and substitute 1) number of antibiotic days or 2) days of therapy for ASI per antibiotic day as our primary predictor, the antibiotic days or DOT variable becomes completely insignificant in the model, which suggests that inclusion of ASI is important and provides information beyond DOT in our fully adjusted model. Furthermore, our ASI per antibiotic day variable fit our model better than DOT alone according to quasi-likelihood information criterion (QIC) values (996 vs 1078) [158].

The goal of this research was to inform antibiotic stewardship activities. Stewardship involves active monitoring and evaluation of antibiotic use as well as enacting interventions designed to achieve an overall reduction in antibiotic use and/or

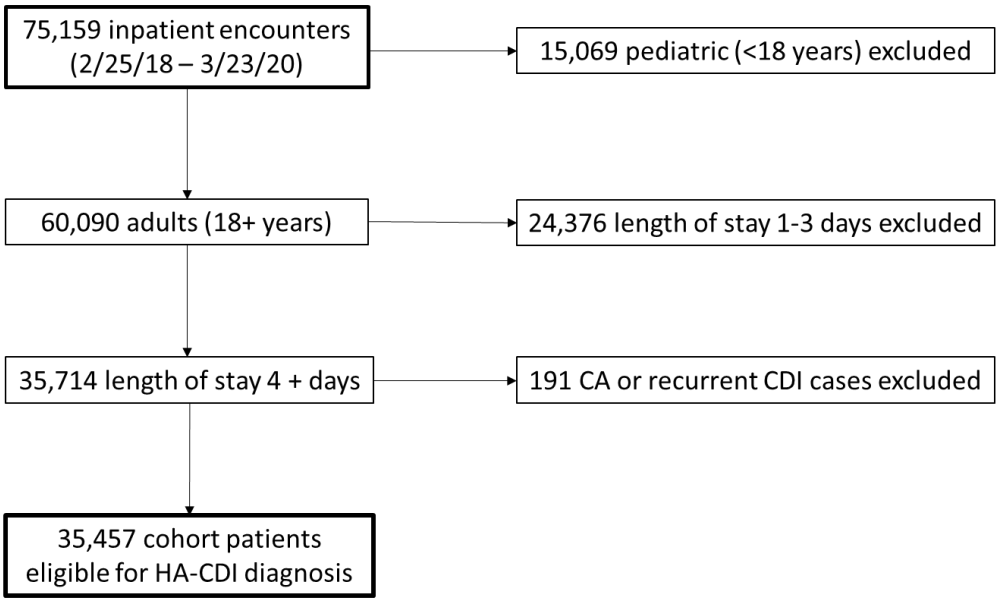
reduction in the use of broad-spectrum antibiotics in favor of narrower-spectrum agents [78, 159]. While early evaluations of ASP interventions focused on process measures and cost, a shift in focus towards clinical and patient-centered outcomes when evaluating ASP interventions has rendered CDI an important clinical outcome due to its strong association with antibiotic therapy in hospital settings [160]. However, evidence has been mixed as to the impact of ASP interventions on CDI incidence. In a meta-analysis by Baur and colleagues, 5 of 11 studies did not report a significant association between ASP interventions and reductions in CDI despite reductions in overall antibiotic use [6]. Another meta-analysis by Mijovic and colleagues reported a significant decrease in CDI incidence in 15 of 24 studies. The authors suggest that reliance on quasi-experimental studies constitutes the main limitation in evaluating the ASP-CDI association [161]. Because CDI risk is multifactorial, with antibiotic therapy, person-to-person-transmission, environmental sources, community acquisition, and medical comorbidity components all contributing to risk, it is difficult to measure the impact of ASP interventions on CDI rates [162]. The context in which these interventions are deployed likely has major impact on the CDI rate; therefore, it is critical that we better understand the causal pathways, attributable risks, and interplay between key risk factors so we can accurately evaluate the likelihood of intervention success. We believe that our study provides valuable addition to the scientific literature in understanding these complexities.

The CDI burden at our institution is relatively low compared to the national burden. In a 2020 meta-analysis, Mara et al. reported an average of 8.3 HA-CDI cases

per 10,000 patient days in the US [10], which is considerably higher than the 4.4 cases per 10,000 patient-days observed at our institution during the study period. Further application of ASI to data from other institutions is necessary to determine the generalizability of our results. However, using ASI allows us to granularly describe the risk of HA-CDI from antibiotics without requiring a large, multifacility dataset. An additional limitation is ASI was not developed specifically for CDI and antibiotics with the same ASI (e.g., clindamycin and sulfamethoxazole-trimethoprim, both with an ASI of 4), could confer very different CDI-specific risks, thus further refinement of the ASI could improve its ability to capture antibiotic-attributable risks for HA-CDI.

We observed that the risk of HA-CDI increases with intensity of antibiotic exposure, as defined by ASI per antibiotic day. Utilizing ASI, and aiming for overall reductions at the facility level, could provide a clear and achievable goal for antibiotic stewardship activities. Additional research is also needed to explore if ASI could also be utilized as a tool for individual-level decision making around prescribing choices. Most existing literature highlights the clinical benefits of empiric prescribing. Our study is among the first to estimate number needed to harm values for commonly used antibiotics and combinations of antibiotics, and provides more complete information on potential adverse implications of antibiotic prescribing. Our study demonstrates that ASI is an excellent predictor of HA-CDI and that ASI provides information beyond days of antibiotic therapy. The antibiotic spectrum index is a valuable tool that can be utilized for evaluation of antibiotic stewardship as well as CDI reduction efforts.

Figure 3.1. Construction of our study cohort (February 25, 2018 – March 23, 2020)



Note: Excluded patients still eligible to contribute to *C. difficile* colonization pressure

Box 3.1. Definition for incident hospital-associated CDI cases

Anti-CDI antibiotic therapy initiated on hospital day four or later	Oral/rectal Vancomycin Metronidazole Fidaxomicin
AND	
Positive laboratory test; sample collected on hospital day four or later	PCR, Stool toxin A, Toxin B
Incident Case Definition	
Non-recurrent – no known CDI in the previous 8 weeks	

Table 3.1. Patient and encounter characteristics in the study cohort by HA-CDI status – January 1, 2018 through March 23, 2020 (N=35,457)

	HA-CDI (n=128)	No CDI (n=35329)
Total patient-days	1879	307715
Sex, n (%)		
Male	66 (51)	16743 (47)
Female	62 (49)	18586 (53)
Age, mean (SD)	58.4 (17.0)	56.4 (19.0)
median (IQR)	62 (48.5-70)	59 (41-71)
Race		
White	112 (88)	30731 (87)
Black	4 (3.0)	932 (2.6)
Asian	5 (3.7)	1012 (2.9)
Other/unknown/ multiple	7 (5.2)	2654 (7.5)
Ethnicity		
Hispanic or Latino	4 (3)	2530 (7)
Not Hispanic or Latino	118 (93)	30481 (86)
Unknown	6 (4)	2318 (7)
Time at-risk, median IQR	11 (7-16.5)	6 (5-9)
Sum of Elixhauser comorbidities	3 (1.5-4)	2 (1-3)
Antibiotics		
Any antibiotic	119 (93)	24107 (68)
No. Antibiotics med, IQR	2 (1-3)	1 (0-2)
Median DOT (IQR)	8 (2-14)	2 (0-7)
Total ASI med (IQR)	42.5 (13.5-80)	8 (0-36)
ASI per DOT mean (SD)	5.4 (2.2)	3.2 (2.6)
med (IQR)	5.5 (4.1-7.2)	3 (0-5)
ASI per day at risk mean (SD)	4.1 (3.0)	2.9 (3.6)
med (IQR)	4 (1.8-5.7)	1.33 (0-4.72)
ASI per antibiotic day mean (SD)	6.9 (3.5)	4.4 (4.1)
med (IQR)	7 (5-9)	3.7 (0-7.4)
Colonization pressure		
Total case-days med (IQR)	10 (4-33)	1 (0-4)
Case-days per day at-risk	1.0 (0.3-1.8)	0.1 (0-0.6)
Other drugs		
PPI or H2RA	109 (85)	19990 (57)
Corticosteroids	50 (39)	8807 (25)
Chemotherapy agents	52 (40)	9372 (27)
Procedures		

Nasogastric tube (NG) placement	30 (23)	3099 (8.8)
Other GI procedures	22 (17)	1445 (4)
Chemotherapy procedures	27 (21)	1917 (5.4)
Admission source		
Non-healthcare or not listed	17 (13)	7036 (20)
ED transfer	25(20)	8582 (24)
Healthcare facility	86 (67)	196711 (56)
Pre-admission risk factors^		
No. prior inpatient encounters		
Zero	117 (91)	30746 (87)
One	11 (9)	3470 (10)
Two or more	0 (0)	1113 (3)
Prior Hospital days		
Zero	117 (91)	30746 (87)
1 to 7	6 (4)	1875 (5)
8+	5 (4)	2708 (8)
Prior Antibiotic days of therapy		
Zero	118 (92)	32099 (91)
1 to 7	5 (4)	1580 (4)
8+	5 (4)	1650 (5)

Abbreviations: IQR, interquartile range; SD, standard deviation; DOT, days of therapy; ASI, antibiotic spectrum index; PPI, proton pump inhibitor; H2RA, H2 receptor antagonist; GI, gastrointestinal; ED, emergency department

^Pre-admission risk factors for the previous 8 weeks at OHSU, excluding the current hospitalization

Table 3.2. Adjusted relative risks for significant CDI risk factors identified in our final model

	Relative Risk (95% CI)
ASI per antibiotic day[a]	1.09 (1.06 – 1.13)
Time at-risk[b]	1.007 (0.998– 1.016)
Number of comorbidities[c]	1.35 (1.22 – 1.50)
PPI/H2RA	2.53 (1.46 – 4.39)
NG tube placement	1.76 (1.06 – 2.93)
GI procedures	2.28 (1.37 – 3.81)
Chemotherapy	2.02 (1.27 – 3.22)
Colonization pressure[d]	2.09 (1.92 – 2.27)

Full model adjusted for the above variables and the following variables that were not significant ($p > 0.05$) in our model: age, number of days hospitalized in the previous 8 weeks, inpatient antibiotic use in the previous 8 weeks, corticosteroid use, and source of hospital admission (Emergency Department, other healthcare facility, non-healthcare); abbreviation: ASI – antibiotic spectrum index, PPI/H2RA – proton pump inhibitor or H2 receptor antagonist, NG – Nasogastric, GI – Gastrointestinal

[a]per unit of ASI per antibiotic day
[b]per day at-risk
[c]per each additional Elixhauser comorbid condition
[d]per case-day of colonization pressure per hospital day

Chapter 3 Appendices

Appendix Table 3.1. Frequency and proportion of antibiotic classes prescribed to inpatients at OHSU – January 1, 2010 through March 23, 2020

Antibiotic class	Frequency of administration	Percent of all antibiotic use
1st generation Cephalosporin	25121	36.2
Penicillin	8229	11.9
3rd generation Cephalosporin	7358	10.6
4th generation Cephalosporin	5413	7.8
Penicillin/beta-lactam	5155	7.4
Macrolide	4882	7.0
2nd generation Cephalosporin	3156	4.5
Fluoroquinolone	2730	3.9
Carbapenem	1615	2.3
Sulfonamide	1383	2.0
Glycopeptide	1217	1.8
Lincomycin	889	1.3
Tetracycline	719	1.0
Antimycobacterial	397	0.6
Other	325	0.5
Nitroimidazole	279	0.4
Aminoglycoside	198	0.3
Lipopeptide	167	0.2
Beta-lactam/monobactam	103	0.2
Oxazolidinone	71	0.1
5th generation Cephalosporin	45	0.1

Appendix Table 3.2. Example antibiotic courses with corresponding risks, risk differences, number needed to harm values and relative risks

	Example antibiotic/antibiotic combination	ASI per antibiotic day value	Estimated risk (95% CI)	Risk difference (95% CI) vs no antibiotic	NNH (95% CI)	Relative risk (95% CI) vs no antibiotic
Avoiding Unnecessary Antibiotic	None	0	0.0020 (0.0014 - 0.0026)			
	Vancomycin or Ceftriaxone	5	0.0031 (0.0026 - 0.0037)	0.0011 (0.0008 - 0.0014)	899 (690 - 1287)	1.55 (1.31 - 1.84)
	Cefepime	6	0.0034 (0.0028 - 0.0040)	0.0014 (0.0010 - 0.0018)	714 (542 - 1046)	1.70 (1.39 - 2.08)
	Piperacillin-Tazobactam or Ciprofloxacin	8	0.0041 (0.0033 - 0.0048)	0.0021 (0.0013 - 0.0028)	486 (359 - 750)	2.03 (1.55 - 2.65)
	Meropenem	10	0.0049 (0.0038 - 0.0059)	0.0028 (0.0017 - 0.0040)	352 (253 - 577)	2.42 (1.73 - 3.39)
	Vancomycin + Cefepime	11	0.0053 (0.0041 - 0.0065)	0.0033 (0.0019 - 0.0046)	304 (216 - 515)	2.64 (1.82 – 3.83)
	Vancomycin + Piperacillin-Tazobactam	13	0.0063 (0.0046 - 0.0081)	0.0043 (0.0024 - 0.0063)	232 (160 - 422)	3.15 (2.03 – 4.88)

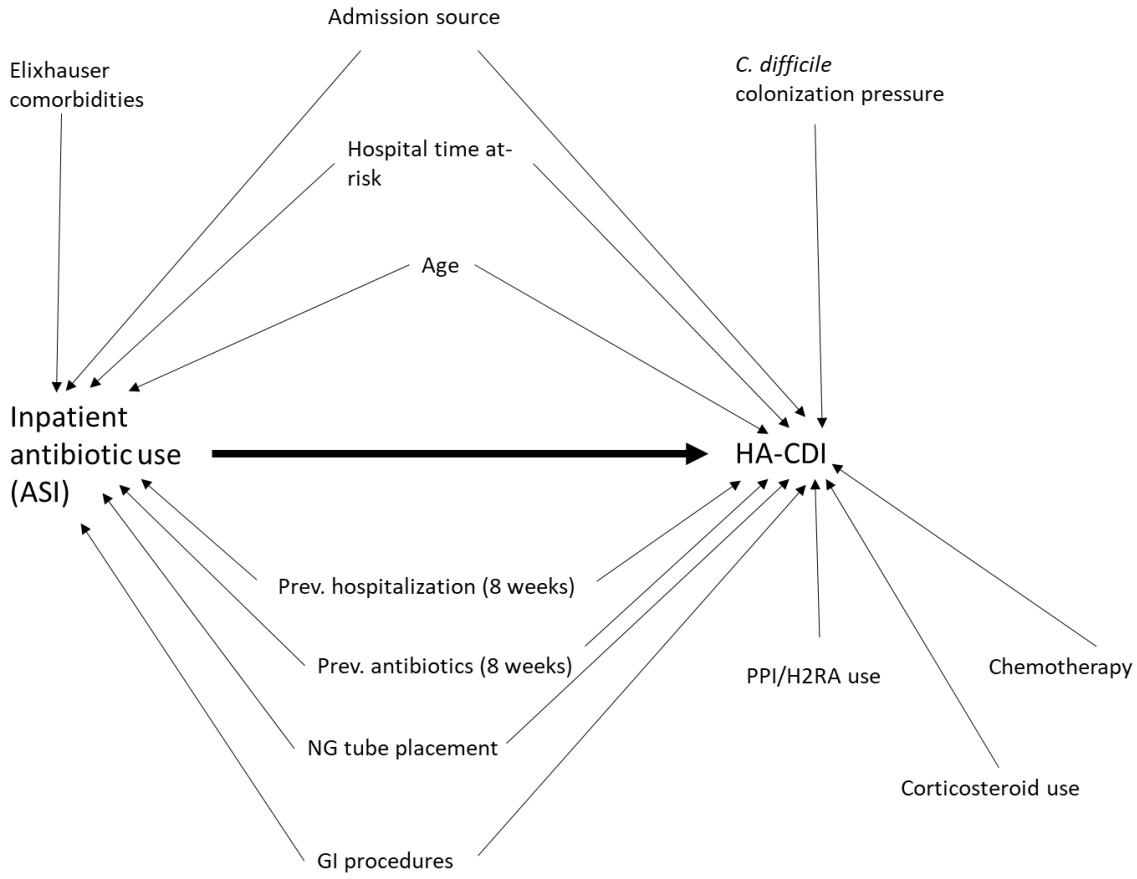
NNH, number needed to harm

Appendix Table 3.3. Risk differences and number needed to harm values for changes in common antibiotic regimens

		Risk difference (95% CI) vs narrower spectrum	**NNH (95% CI)**
De-escalation on Day 3 to narrower spectrum	Piperacillin-Tazobactam to Ceftriaxone*	0.0009 (0.0055 - 0.0013)	1057 (747 - 1808)
	Meropenem to Ceftazidime*	0.0017 (0.0010 - 0.0025)	578 (398 - 1053)
Mono vs combination therapy	Ceftriaxone + Azithromycin vs Azithromycin only[#]	0.0016 (0.0092 - 0.0022)	633 (445 - 1086)

*7-days total
[#]5-day course

Appendix Figure 3.1. Directed acyclic graph depicting proposed causal associations between variables included in our final model



Note: Arrows depicting causal associations between covariates have been omitted

Appendix Box 3.1. Antibiotic Spectrum Index (ASI) values for each antibiotic [150]

Antibiotic Agent Name	Antibiotic Class	ASI Score
Dicloxacillin	Penicillin	1
Oxacillin	Penicillin	1
Nafcillin*	Penicillin	1
Amoxicillin	Penicillin	2
Ampicillin	Penicillin	2
Cephalexin	1st gen Cephalosporin	2
Erythromycin	Macrolide	2
Metronidazole	Nitroimidazole	2
Penicillin	Penicillin	2
Cefadroxil*	1st gen Cephalosporin	2
Aztreonam	Beta-lactam/monobactam	3
Cefazolin	1st gen Cephalosporin	3
Cefdinir	3rd gen Cephalosporin	3
Cefixime	3rd gen Cephalosporin	3
Cefpodoxime	3rd gen Cephalosporin	3
Rifampin	Antimycobacterial	3
Rifaximin*	Antimycobacterial	3
Azithromycin	Macrolide	4
Cefprozil	2nd gen Cephalosporin	4
Ceftazidime	3rd gen Cephalosporin	4
Cefuroxime	2nd gen Cephalosporin	4
Chloramphenicol	Other	4
Clarithromycin	Macrolide	4
Clindamycin	Lincomycin	4
Piperacillin	Penicillin/beta-lactam	4
Sulfamethoxazole-Trimethoprim	Sulfonamide	4
Dalbavancin*	Glycopeptide	4
Cefotaxime	3rd gen Cephalosporin	5
Cefoxitin	2nd gen Cephalosporin	5
Ceftriaxone	3rd gen Cephalosporin	5
Colistin	Other	5
Daptomycin	Lipopeptide	5
Doxycycline	Tetracycline	5
Gentamicin	Aminoglycoside	5
Minocycline	Tetracycline	5
Telavancin	Lipoglycopeptide	5
Tobramycin	Aminoglycoside	5
Vancomycin	Glycopeptide	5
Oritavancin*	Glycopeptide	5
Tetracycline*	Tetracycline	5
Polymyxin*	Other	5
Amikacin	Aminoglycoside	6
Amoxicillin-Clavulanate	Penicillin/beta-lactam	6
Ampicillin-Sulbactam	Penicillin/beta-lactam	6
Cefepime	4th gen Cephalosporin	6

Linezolid	Oxazolidinone	6
Ticarcillin-Clavulanate	Penicillin/beta-lactam	6
Nitrofurantoin*	Other	6
Fosfomycin*	Other	7
Ceftaroline	5th gen Cephalosporin	8
Ciprofloxacin	Fluoroquinolone	8
Piperacillin-Tazobactam	Penicillin/beta-lactam	8
Ceftazidime-Avibactam*	Cephalosporin/beta-lactam	8
Ertapenem	Carbapenem	9
Levofloxacin	Fluoroquinolone	9
Meropenem	Carbapenem	10
Moxifloxacin	Fluoroquinolone	10
Imipenem-Cilastatin	Carbapenem	11
Tigecycline	Glycylcycline	13

*Agents not in original ASI paper, added by our group

Appendix Box 3.2. Proton pump inhibitors and H2-receptor antagonists

Prescription Proton Pump Inhibitor (PPI) Drugs		**Prescription H2-Receptor Antagonist Drugs**	
Generic name	**Brand name(s)**	**Generic name**	**Brand name(s)**
dexlansoprazole	Dexilant	cimetidine	Tagamet
esomeprazole magnesium	Nexium	famotidine	Pepcid, Duexis
esomeprazole magnesium and naproxen	Vimovo	nizatidine	Axid, Nizatidine
lansoprazole	Prevacid	ranitidine	Zantac, Tritec
omeprazole	Prilosec	**Over-the-Counter H2-Receptor Antagonist Drugs**	
omeprazole and Sodium bicarbonate	Zegerid	cimetidine	Tagamet HB
pantoprazole sodium	Protonix	famotidine	Pepcid Complete, Pepcid AC
rabeprazole sodium	AcipHex	nizatidine	Axid AR
Over-the-Counter Proton Pump Inhibitor (PPI) Drugs		ranitidine	Zantac
lansoprazole	Prevacid 24HR		
omeprazole magnesium	Prilosec OTC		
omeprazole and sodium bicarbonate	Zegerid OTC		
omeprazole	Omeprazole		

Source: [163]

Appendix Box 3.3. Immunosuppressants

Immunosuppressant category	Name
Corticosteroids	prednisone
	budesonide
	prednisolone
Janus kinase inhibitors	tofacitinib
Calcineurin inhibitors	cyclosporine
	tacrolimus
mTOR inhibitors	sirolimus
	everolimus
IMDH inhibitors	azathioprine
	leflunomide
	mycophenolate
Monoclonal antibodies	basiliximab
	daclizumab
Biologics	adalimumab [Humira]
	etanercept [Enbrel]
	ixekizumab [Taltz]
	secukinumab [Cosentyx]

Source: [164]

Appendix Box 3.4. List of procedures associated with CDI risk

Procedure	Description
Active chemotherapy	ICD-10-PCS Z51.1z (Encounter for antineoplastic chemotherapy and immunotherapy)
	Chemotherapy CPT code 96400, 96408 to 96425, 96520, and 96530
Nasogastric tube placement	ICD-10 0DH673Z (Insertion of infusion device into stomach, via natural or artificial opening)
	CPT code 43752
Other gastrointestinal procedures	OD* ICD-10-PCS parent code

Source: www.icd10data.com

Chapter 4: Examining the impact of the COVID-19 pandemic on hospital-associated *Clostridioides difficile* infection

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4.1 Abstract

4.1.1 Objective

To evaluate the impact of changes in the size and characteristics of the hospitalized patient population during the COVID-19 pandemic on the incidence hospital-associated *Clostridioides difficile* infection (HA-CDI).

4.1.2 Design

Interrupted time-series analysis.

4.1.3 Setting

A 576-bed academic medical center in Portland, Oregon.

4.1.4 Methods

We established March 23, 2020 as our pandemic onset and included 24 pre-pandemic and 24 pandemic-era 30-day intervals. We built an autoregressive segmented regression model to evaluate immediate and gradual changes in HA-CDI rate during the pandemic while controlling for changes in known CDI risk factors.

4.1.5 Results

We observed 4.5 HA-CDI cases per 10,000 patient-days in the two years prior to the pandemic and 4.7 cases per 10,000 patient-days in the first two years of the pandemic. According to our adjusted segmented regression model, there were neither significant changes in HA-CDI rate at the onset of the pandemic (level change coefficient = 0.70, p-value = 0.57) nor over time during the pandemic (slope change coefficient = 0.003, p-value = 0.97). We observed significant increases in frequency and intensity of antibiotic use, time at risk, comorbidities, and patient age before and after the pandemic onset. Frequency of *C. difficile* testing did not significantly change during the pandemic (p = 0.72).

4.1.6 Conclusions

Despite large increases in several CDI risk factors, we did not observe the expected corresponding changes in HA-CDI rate during the first two years of the COVID-19 pandemic. We hypothesize that infection prevention measures responding to COVID-19 played a role in CDI prevention.

4.2 Introduction

Hospital-associated *Clostridioides difficile* infection (HA-CDI) manifests as severe diarrheal illness and is a major source of global morbidity and mortality, with an estimated 3.54 cases per 10,000 patient days and a 50 percent increase in mortality compared to those without CDI [9, 11]. In the hospital setting, the spore-forming *C. difficile* is challenging to eliminate from the environment, thus making hand hygiene, use of personal protective equipment (PPE), and environmental cleaning crucial components to mitigating HA-CDI. The primary patient-level modifiable risk factor for HA-CDI is antibiotic use, as exposure to broad-spectrum antibiotic therapy can increase the risk of CDI up to four-fold [72]. Thus, HA-CDI is a frequently measured outcome in evaluations of interventions aimed at optimizing inpatient antibiotic use [31, 69-72].

Though HA-CDI has been extensively studied, the COVID-19 pandemic significantly altered the healthcare context, particularly during the onset of the pandemic. In the United States, April through June 2020 saw a 150 percent decrease in hospital admissions, and a 40 percent increase in ICU admissions. With this came nearly a 50 percent increase in all-cause in-hospital deaths, a third of which were COVID-19-related [114, 115]. A national survey of clinicians aiming to describe the changing healthcare landscape reports frequent staffing shortages, repurposing of non-ICU beds to ICU beds, and overall substandard care for non-COVID-19 patients relative to COVID-19 patients [117]. These changes also resulted in a shift in the hospitalized patient case-mix that directly influenced both modifiable and non-modifiable risk factors providing an opportunity to study the impact of these case-mix changes on the risk of CDI. This

includes changes in the frequency of patients with advanced age, immunosuppression, use of acid suppressing medication, and comorbid conditions [2]. Understanding this changing context can provide new insight into the complex epidemiology of HA-CDI.

Our study objectives were to describe changes in HA-CDI rate after healthcare changes due to the COVID-19 pandemic and to determine the relative importance of the contextual factors likely associated with CDI. We hypothesized that we would see an increase in HA-CDI rate at the onset of the pandemic due to increases in antibiotic use, followed by a gradual return to the baseline rate.

4.3 Methods

4.3.1 Setting and study design

We conducted an interrupted time-series analysis using retrospective healthcare data from Oregon Health & Science University (OHSU) Hospital, a 576-bed academic hospital in Portland, OR. We collected medical record data from our institution's research data repository for inpatient visits between January 2018 and April 2022. We limited our analysis to adult (≥ 18 years) inpatients and excluded patients with hospital stays under 4 days and those known to have recurrent (CDI in the previous 8 weeks) or community-acquired (CDI diagnosis within first 3 days of hospitalization) CDI. We aggregated data into 30-day periods to ensure we were evaluating uniform time intervals. This project was approved by OHSU's Institutional Review Board (OHSU IRB #23278).

4.3.2 Interruption timepoint

We established March 23, 2020 as our primary interruption timepoint (hereafter referred to as “pandemic onset”), the date the Oregon Governor issued an executive order prohibiting elective and non-urgent procedures as well as non-essential visitation [111]. We established the 24 30-day intervals prior to the interruption point as our “pre-pandemic” period, beginning March 4, 2018, and an equal number of 30-day intervals after the interruption point as our post-interruption, “pandemic era” period ending March 13, 2022. We also evaluated the following dates as secondary interruption points during the pandemic: initial vaccine rollout (December 18, 2020), start of “pandemic year 2” (March 23, 2021), delta wave start (June 1, 2021), and omicron wave start (December 20, 2021) [165].

Our primary outcome was incident, non-recurrent HA-CDI per 10,000 patient-days for each time period. We identified incident, non-recurrent cases of HA-CDI using a previously validated combination of medication and laboratory testing data [153]. Incident CDI cases were hospital-associated if the onset date, defined as the date of first anti-*C. difficile* antibiotic administration or stool specimen sample collection from the positive *C. difficile* laboratory test, whichever occurred first, occurred on hospital day 4 or later. This is consistent with the National Healthcare Safety Network (NHSN) definition [166]. We considered cases non-recurrent if no prior CDI events were identified at the index facility in the 8 weeks before the initial CDI diagnosis. We then aggregated HA-CDI counts into 30-day intervals and divided by number of patient days to get our primary outcome variable (HA-CDI cases per 10,000 patient-days).

4.3.3 Antibiotic prescribing

To capture information about intensity of antibiotic therapy, we utilized the antibiotic spectrum index (ASI) developed by Gerber et al. [150]. ASI assigns and sums point values (ranging from 1 to 13) based on each agent's activity against a variety of bacterial species. Higher ASI values represent broader spectrum antibiotics. We calculated each hospitalized patient's ASI per antibiotic day by summing ASI scores for each individual agent a patient was exposed to across all days of therapy and then dividing by the number of hospital days during which a patient received at least one antibiotic. We then aggregated this value for each study time interval.

4.3.4 Other CDI risk factors

We examined other known CDI risk factors including time at-risk [10], age [2, 88], number of comorbid conditions (defined by Elixhauser comorbidity index [167])[87, 88], days hospitalized in the previous 8 weeks [20, 102], inpatient antibiotic use in the previous 8 weeks [93]; proton pump inhibitor or H2 receptor antagonist use [87-89], nasogastric tube placement [71, 88, 89], other gastrointestinal procedures [71], corticosteroid use [87], or chemotherapy (yes or no) [2]; source of hospital admission (Emergency Department, other healthcare facility, non-healthcare) [11, 106], and *C. difficile* colonization pressure (total case-days) [67, 68] We defined colonization pressure as the total daily number of patients with CDI present in the same ward during each patient's time at risk. A patient with CDI or colonized with *C. difficile* was eligible to contribute to colonization pressure for the 14 days after initiation of first CDI treatment or until discharge. We summed the daily number of patients with CDI by hospital ward

for every day a patient was present on the ward (*case-days* of colonization pressure [68]) and aggregated covariates into 30-day intervals.

4.3.5 Statistical analysis

We performed segmented autoregressive linear regression to examine the pre-interruption trend in HA-CDI rate, as well as post-interruption *slope/trend* change and *level* change using SAS v 9.4 (Cary, NC). We examined model parameter estimates and p-values to assess the evidence of slope and/or level changes in HA-CDI rate after the pandemic's onset.

To assess changes in slope and level for known HA-CDI risk factors, we generated identical segmented regression models with each risk factor as the dependent variable using the same parameters described above for the HA-CDI model. Any CDI risk factors with slope or level-change p-values greater than 0.15 were considered for inclusion in a multivariable model describing changes in HA-CDI rate over time. We then fit a multivariable model using the Akaike Information Criterion (AIC) and total R^2 values to assess model fit, minimizing the former and maximizing the latter. Variables for pre-pandemic trend, the pre- post-indicator variable, and pandemic-era trend were always included in the model.

Finally, we examined the frequency of *C. difficile* laboratory testing on a per encounter basis to ensure that testing did not change at pandemic's onset, which could introduce detection bias. We also examined test positivity (i.e., the proportion of

positive tests among all tested) to identify any significant *C. difficile* trends not captured by our HA-CDI case definition.

4.4 Results

We identified 254 cases of HA-CDI over the entire study period, corresponding to an overall rate of 4.2 cases per 10,000 patient-days (standard deviation (SD) = 2.2). In the pre-pandemic period, there were 137 HA-CDI cases identified, or 4.5 cases per 10,000 patient-days (SD = 1.8). There were 81 cases in the pandemic era, or 4.7 per 10,000 patient-days (SD = 3.2). Table 4.1 outlines patient characteristics for the two time periods. There was a significant decrease in the mean number of admissions per 30-day period with the onset of the pandemic (1441 vs 894) (Table 4.2, Appendix Figure 4.1). The pandemic-era patient population was, on average, older than the pre-pandemic population (57.8 vs 56.5 years) and had slightly longer average lengths of stay (9.2 days vs 8.8 days). We also observed a decrease in average case-days of colonization pressure per period (3.9 vs 1.1).

4.4.1 Changes in HA-CDI risk factors

According to our unadjusted autoregressive segmented regression model, there were neither significant immediate changes in HA-CDI rate at the onset of the pandemic (level change coefficient = -0.88, p = 0.36), nor were there significant changes in pandemic-era slope over time (slope change coefficient = 0.09, p = 0.18). We did observe significant changes in several CDI risk factors (Table 4.2), including intensity and

frequency of antibiotic therapy. This includes a level increase in antibiotic spectrum index per antibiotic day (0.46 ASI points per antibiotic day, Table 4.2), and a slope (0.02 additional antibiotic days per encounter per interval) and level (0.24 additional antibiotic days per encounter) increase in number of antibiotic days per encounter (Table 4.2).

We observed an increase in the mean number of comorbid conditions (0.11 additional comorbidities, on average) at the pandemic's onset followed by a gradual return to the pre-pandemic mean (Appendix Figure 4.2). We did not observe any immediate level changes in mean time at-risk, but we did observe a significant pandemic-era slope increase (0.06 additional days per interval). We observed a small level decrease in case-days of colonization pressure throughout our entire study period (1.03 fewer case-days), yet the observed level decrease could be due to chance (p = 0.09) (Table 4.2).

4.4.2 Multivariable segmented regression results

The multivariable model included average case-days of colonization pressure per 30-day period, average ASI per antibiotic day, and average number of comorbid conditions (Figure 4.2). After adjusting for colonization pressure, ASI per antibiotic day, and mean number of comorbidities, there was no immediate change in HA-CDI at the pandemic's onset (level change coefficient = 0.70, p-value = 0.57) nor was there a change in slope (slope change coefficient = 0.003, p-value = 0.97).

4.4.3 C. difficile testing

We evaluated the frequency of *C. difficile* testing over time to assess the potential for detection bias. While there was an initial drop in the total volume of *C. difficile* testing at the onset of the pandemic, (level change coefficient = -15.6, p-value = 0.003), mean testing frequency increased on a per-encounter basis (pre/post mean 5.2 vs 5.7, level change coefficient = 0.82, p-value = 0.04). There was a slight level decrease in the percentage of positive *C. difficile* tests (level change coefficient = -2.5, p-value = 0.11) (Table 4.2, Appendix Figure 4.3), though test positivity increased significantly as the pandemic progressed (slope change coefficient = 0.27, p = 0.03).

4.4.4 Evaluation of additional interruption time points

Inspection of our time series data suggested an increase in HA-CDI trend approximately one year into the pandemic (Figure 4.1). Thus, we evaluated an additional interruption point at the start of pandemic year 2 within the final regression model. We observed a significant slope increase in our final 12 time intervals (slope change coefficient = 0.36, p = 0.005). Adding the terms for the second pandemic-era period also explained more variability in our time series data (R-squared 0.56 vs 0.47) (Figure 4.3). None of the other secondary interruption points evaluated yielded significant results.

4.5 Discussion

Despite clear and consistent increases in CDI risk factors at the onset of the COVID-19 pandemic, we did not observe significant changes in HA-CDI rate. The

increases in key HA-CDI risk factors included frequency and intensity of antibiotic use, patient comorbidity burden, and time at-risk. We also saw a slight level decrease in case-days of *C. difficile* colonization pressure at the pandemic's onset, though the observed change could be due to chance.

Including an additional interruption point one year into the pandemic improved model fit and suggests a trend increase in HA-CDI rate during the second pandemic period. A possible explanation is that vaccination of healthcare workers and patients could have again altered the healthcare environment. However, because of vaccine availability and the tiered rollout, it is difficult to establish a pre- and post-vaccine period as a specifically defined interruption time point. OHSU began vaccinating all staff, students, and volunteers in January of 2021. Approximately 25% of the Oregon population had received at least one dose of the vaccine in March of 2021 [168]. As of October 2021, 96 percent of OHSU employees, students, and volunteers were fully vaccinated [169].

The significant increase in ASI per antibiotic day is noteworthy. Though the proportion of patients receiving any inpatient antibiotic did not change, antibiotics were administered on more calendar days during the pandemic era compared to pre-pandemic at our institution. Thus, the only way to observe increases in this variable would be the prescribing of broader spectrum agents or a greater number of separate agents on the same calendar day. This can be interpreted as an increase in the intensity of antibiotic therapy at the onset, and throughout the pandemic. While we would expect a corresponding increase in HA-CDI, that is not what we observed. Current literature on

antibiotic use during the pandemic shows a great deal of heterogeneity. During the pandemic, there were documented shifts in antibiotic utilization for suspected COVID-19 cases. Overall antibiotic use in hospitals increased early in the pandemic, with a 5 percent increase in overall antibiotic prescribing and a 22 percent increase in ceftriaxone compared to the same time in 2019. Prescribing then leveled off, though use remained high as the pandemic progressed, according to data from NHSN [118]. Among confirmed COVID-19 patients, empiric treatment using broad-spectrum agents was initially common due to concerns for bacterial superinfection[120], likely influenced by similar practice patterns for patients admitted with community-acquired pneumonia [121]. Additionally, over the course of the pandemic, different treatment options, including antibiotics, were explored in an attempt to mitigate COVID-19's high mortality rate [120].

The steady decrease in colonization pressure is potentially a key finding that could explain our observed HA-CDI rate. We have previously reported that colonization pressure contributes to HA-CDI risk [170, 171]. The decrease in colonization pressure is likely due to a smaller patient population and potentially less patient movement during the pandemic. In a *post hoc* analysis, we observed a steep and significant decline in patient movement (defined by number of physical hospital locations per patient-day) during the first year of the pandemic. There was then a level increase at the start of pandemic year 2, though not back to pre-pandemic levels (Appendix Figure 4.4). An opposing force to this drop in colonization pressure is longer patient lengths of stay, which could increase an individual's possibility of either contributing to or experiencing

colonization pressure. Unmeasured colonization pressure from colonized patients could also be a factor. Potential changes in *C. difficile* colonization pressure during the COVID-19 pandemic merits further study.

One concern for bias is a possible decrease in *C. difficile* testing during the pandemic due to resources and personnel being diverted elsewhere. Although we did find a decrease in the overall volume of *C. difficile* testing, there was an increase in testing on a per encounter basis. This mitigates the concern for detection bias. We also saw a non-significant decrease in *C. difficile* test positivity (level change coefficient = -2.8, p-value = 0.11) and a significant slope in increase in positivity (slope change coefficient = 0.27, p-value = 0.03).

Our study contributes to the growing body of literature around the pandemic's impact on the healthcare environment. A time-series analysis conducted by Aldeyab and colleagues at a mid-sized hospital in Ireland reported that a stewardship program aimed at reducing the use of high-risk antibiotics successfully reduced use of these agents as well as CDI incidence [172]. In contrast, our analysis indicated that increases in antibiotic use were not associated with an increase in CDI incidence, providing evidence that there are other key risk factors at play. A retrospective cohort study by Desai et al. examined antibiotic prescribing during the first 11 months of pandemic and observed an initial spike in overall prescribing, which tapered off as the pandemic progressed. The authors suggest that this was driven by prescribing in COVID-19 patients, as guidelines to the contrary had yet to be published [173]. Nandi and colleagues performed a global cost analysis across 71 countries and highlight a decrease in sales of broad-spectrum

antibiotics in April and May of 2020, followed by a gradual increase to pre-pandemic levels [174]. Based upon data from NHSN, the CDC reported increased overall inpatient prescribing at the onset of the pandemic, but overall lower prescribing in 2021 compared to 2019 [175]. NSHN also reports that outpatient antibiotic prescribing decreased at the onset of the pandemic and then rebounded to pre-pandemic levels [176]. CDC also reported a decrease in the CDI LabID standardized infection ratio (SIR) across the first 4 quarters of 2020. This is in contrast to consistent increases in the SIR for other healthcare-associated infections, including MRSA bacteremia, and catheter, central line, and ventilator-associated events [177]. We did not observe the same decrease in CDI in our institution.

This study utilized a comprehensive, longitudinal dataset with complete laboratory and pharmacy information that allowed us to apply an accurate case definition for HA-CDI that our group has previously validated [153]. We also have complete patient location data, which allows us to calculate colonization pressure. Although the interrupted time series design is a strong quasi-experimental study design, the nature of group level data limits this study's capacity for causal inference. Our institution is also a low CDI incidence environment compared to the national average (4.2 vs 8.3 cases per 10,000 patient-days per Marra et al.) [10], which could limit our statistical power and overall generalizability. This could also explain why examining the onset of the delta and omicron COVID-19 variant waves did not yield significant results. Finally, we did not have data on actual infection prevention efforts, so this could not be directly evaluated within our regression model.

While the association between antibiotic use and HA-CDI is well established, it is clear that the effect of changes in antibiotic exposure on CDI is very sensitive to the healthcare context, such as shifts in hospital population characteristics resulting in a presumably sicker, more vulnerable-to-CDI patient population than prior to the pandemic at many facilities. Therefore, our study raises the hypothesis that COVID-19 prevention measures, such as a heightened focus on handwashing, enhanced PPE use, and enhanced environmental cleaning procedures might have prevented HA-CDI. While there was some evidence of an increase in year 2 of the pandemic, more follow-up time across multiple facilities is required to further examine this possible trend.

Table 4.1. Patient attributes before (March 4, 2018 to March 23, 2020) and during the first two years (March 24, 2020 to March 13, 2022) of the COVID-19 pandemic

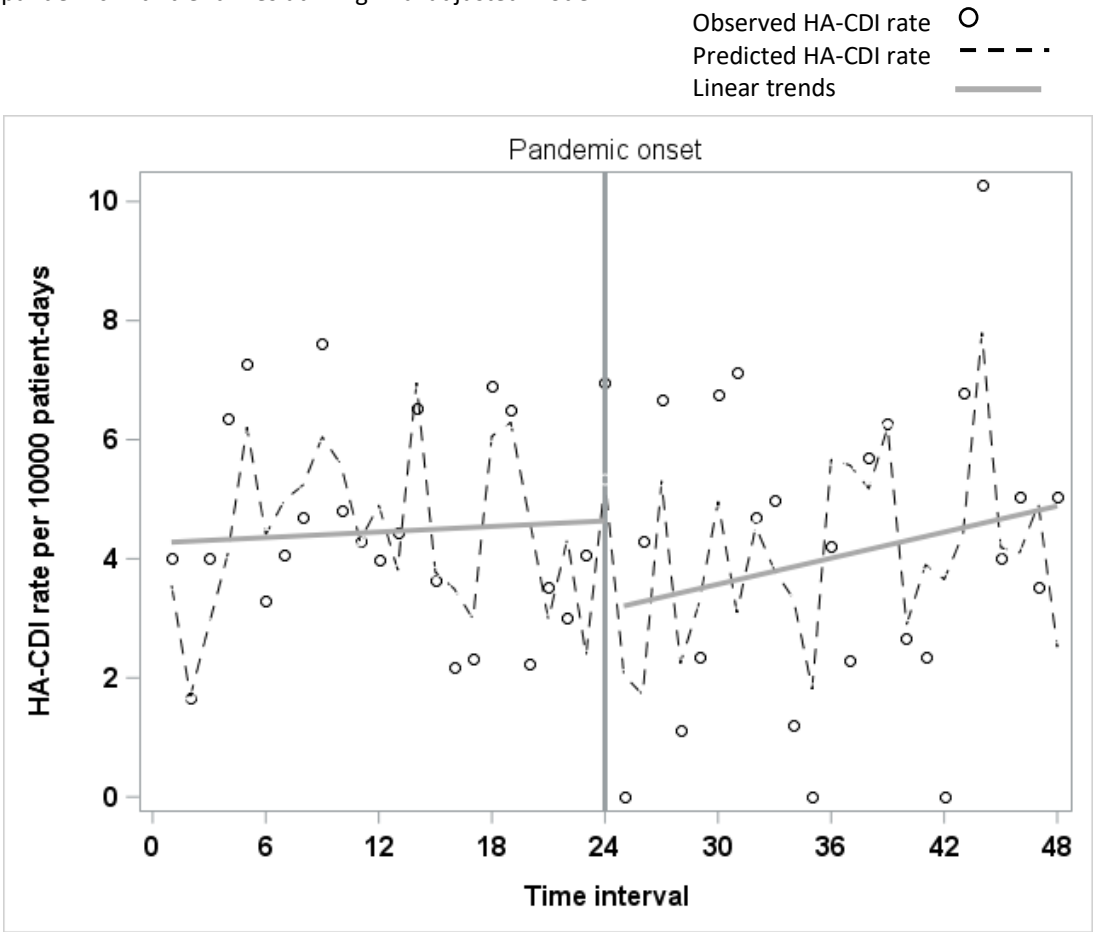
Patient characteristic	Pre-pandemic	Pandemic era
Female sex (%)	52.7	53.3
White race (%)	87.1	85.9
Hispanic ethnicity (%)	7.4	7.7
Age (mean)	56.5	57.8
Number of comorbidities (mean)	1.96	2.01
Inpatient antibiotic use (%)	68.3	67.8
Transferred from ED (%)	24.1	16.8
Inpatient PPI or H2RA (%)	5.7	5.9
Chemotherapy procedures (%)	5.5	4.3
Nasogastric tube placement (%)	8.8	8.6
Any gastrointestinal procedure (%)	4.1	3.4

Abbreviations: ED, emergency department; PPI, proton pump inhibitor; H2RA, H2-histamine receptor antagonist

Table 4.2. Pre-COVID-19 pandemic (March 4, 2018 to March 23, 2020) and pandemic-era (March 24, 2020 to March 13, 2022) means, slope, and level changes for HA-CDI and key risk factors

	Pre-period mean	Pandemic-era mean	Immediate pandemic-era change (95% confidence interval)	Pandemic-era trend change (95% confidence interval)
ASI points per antibiotic day	4.4	4.84	0.46 (0.33, 0.58)	-0.01 (-0.02, -0.003)
Number of antibiotic days per encounter	3.96	4.41	0.24 (0.01, 0.47)	0.02 (0.001, 0.034)
Days of therapy per encounter	5.78	7.24	1.12 (0.70, 1.54)	0.03 (-0.004, 0.05)
Admissions per month	1441	894	-444 (-585, -303)	-0.46 (-16.8, 15.9)
Time at-risk (days)	8.76	9.19	-0.02 (-0.42, 0.37)	0.06 (0.03, 0.09)
Number of comorbidities	1.96	2.01	0.11 (0.04, 0.18)	-0.010 (-0.01, -0.004)
Patient age (years) at admission	56.5	57.8	0.81 (-0.21, 1.83)	-0.09 (-0.18, 0.00)
Total case-days of colonization pressure	3.91	1.09	-1.03 (-2.171, 0.12)	0.05 (-0.04, 0.14)
HA-CDI rate (per 10,000 patient-days)	4.52	4.06	-0.88 (-3.84, 1.27)	0.09 (-0.11, 0.26)
***C. difficile* tests (count)**	74.5	50.6	-15.62 (-25.3, -5.9)	0.03 (-0.67, 0.72)
***C. difficile* tests (per 100 admitted patients)**	5.18	5.65	0.82 (0.06, 2.57)	-0.01 (-0.06, 0.04)
***C. difficile* test positivity (percent)**	7.58	6.67	-2.85 (-0.23, 0.11)	0.27 (0.03, 0.50)

Figure 4.1. Time series of HA-CDI rate before and throughout the first two years of the COVID-19 pandemic with trendlines utilizing final adjusted model



R^2 = 0.47; adjusted for ASI per antibiotic day, case-days of colonization pressure, sum of comorbidities

Figure 4.2. Time series overlay of HA-CDI rate and ASI per antibiotic day before and during the pandemic

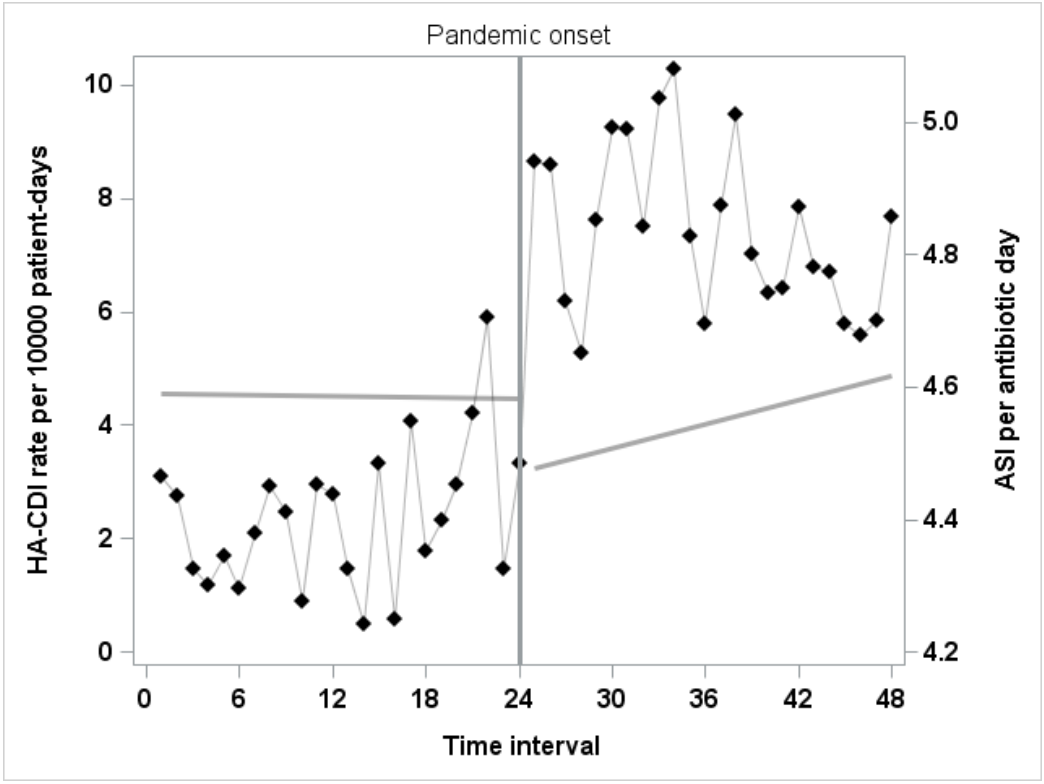
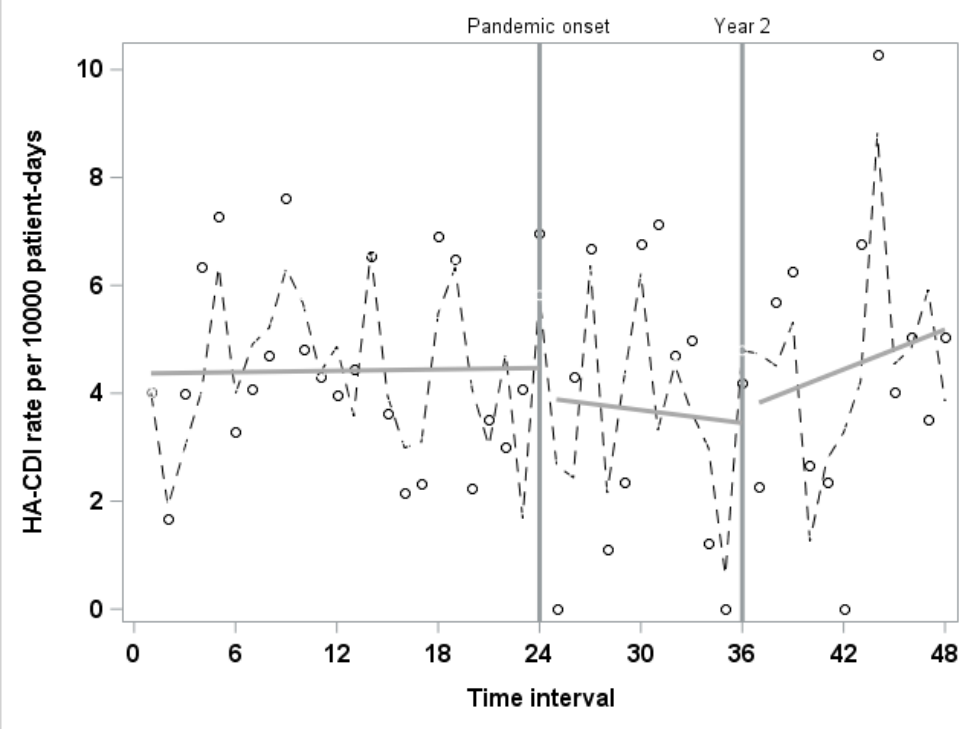


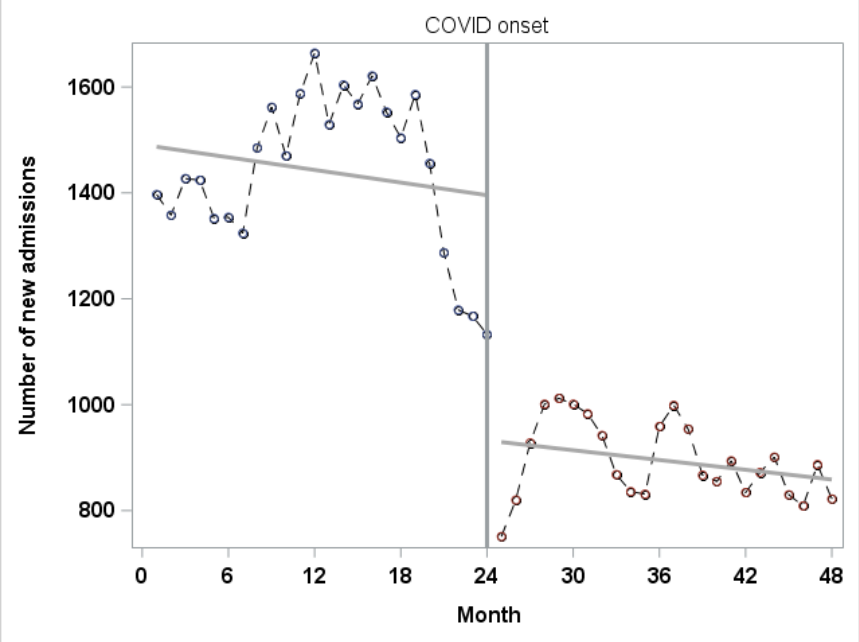
Figure 4.3. Results of segmented regression model with an additional interruption point at pandemic year 2



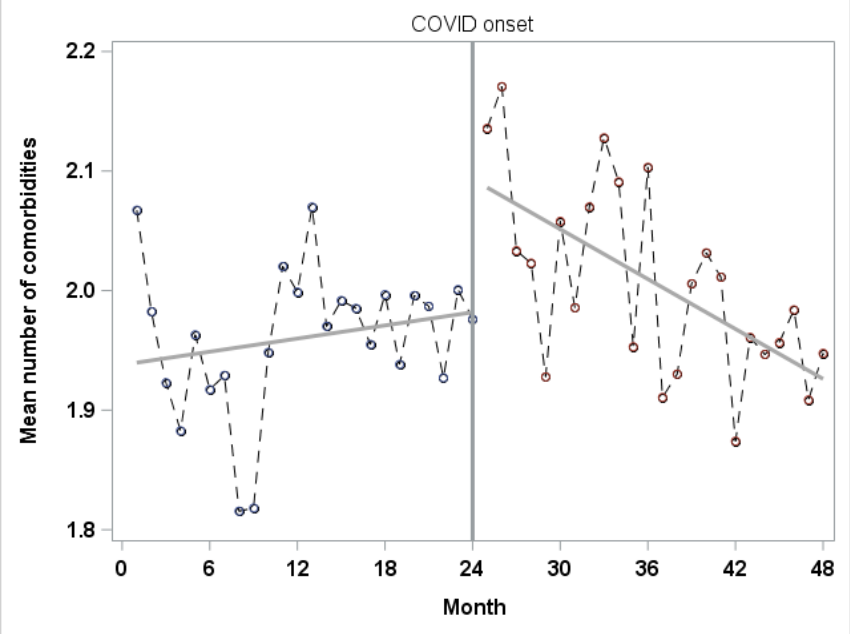
R^2 = 0.56; p-value for year 2 trend change = 0.005

Chapter 4 Appendices

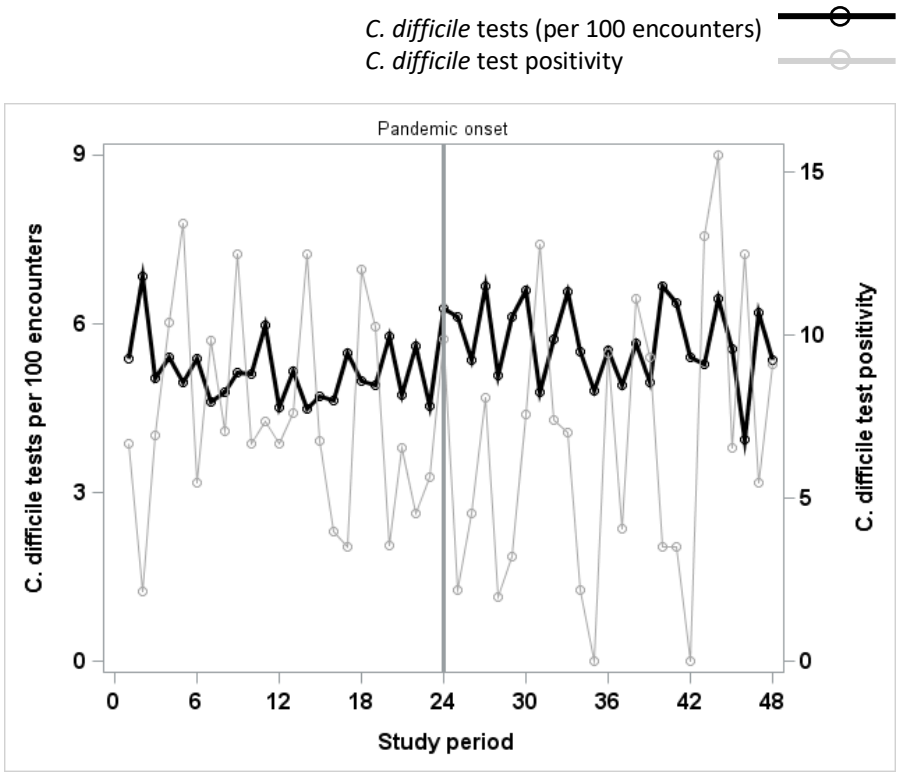
Appendix Figure 4.1. Time series and trendlines for number of new admissions per time period before and during the pandemic



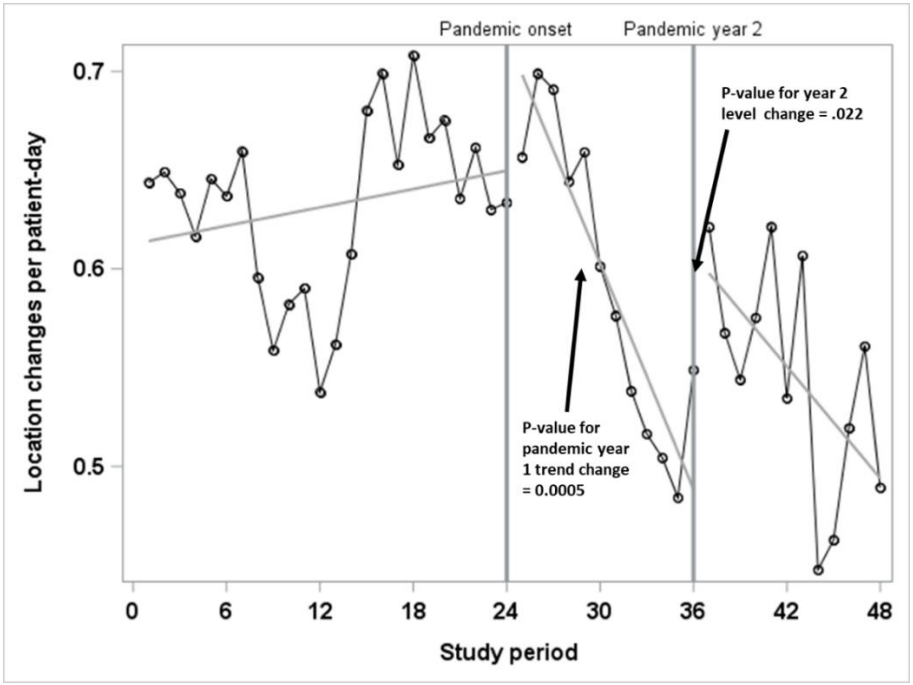
Appendix Figure 4.2. Time series and trendlines for mean number of comorbid conditions per time period before and during the pandemic



Appendix Figure 4.3. Time series overlay of *C. difficile* test per 100 encounters and *C. difficile* test positivity



Appendix Figure 4.4. *Post hoc* time series analysis of number of physical hospital location changes per patient-day.



Chapter 5: Evaluating antimicrobial stewardship interventions and the impact of hospital-associated *Clostridioides difficile* infection: a mathematical modeling study

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5.1 Abstract

Clostridioides difficile infection is a major source of morbidity and mortality worldwide. Because broad-spectrum antibiotic prescribing is a primary risk factor, hospital-associated *C. difficile* infection (HA-CDI) is often employed as a metric for evaluating reductions in antibiotic use following antimicrobial stewardship interventions. However, studies examining the utility of HA-CDI as a metric for stewardship have often been underpowered and inconclusive. We created a stochastic mathematical model, which we parameterized using Oregon Health & Science University data when possible and empirical literature otherwise. The purpose of our model was to evaluate the association between changes in high-risk antibiotic use and HA-CDI following hypothetical stewardship interventions in a 500-bed acute care hospital across a variety of scenarios, including fluctuations in types of admitted patients (high/low risk, *C. difficile* colonized/uncolonized) and in-hospital *C. difficile* transmission. We utilized the antibiotic spectrum index (ASI) per antibiotic day to incorporate information on intensity of antibiotic therapy and simulated 365 hospital days. Our model simulated an average HA-CDI incidence rate of 7.47 cases per 10,000 patient-days (95% confidence interval: 7.42 – 7.52) using our baseline parameters and 1,000 simulations. Patients were in the hospital for 5.5 days, on average. Incremental decreases in high-risk antibiotic use (5%, 10%, 15% decrease in ASI per antibiotic day) were directly proportional to reduced HA-CDI incidence in 6 of the 7 hospital settings we evaluated. In instances of high prior-to-admission antibiotic use, reductions in antibiotics after stewardship no longer were reflected by changes in HA-CDI incidence (p-value for difference in mean 0.8). Thus, it is

important to consider pre-admission factors and regional contexts when deciding to use HA-CDI incidence as a metric for antimicrobial stewardship success.

5.2 Introduction

As much as half of antibiotics prescribed in US hospitals and clinics are inappropriate or altogether unnecessary [3, 4]. In response, the United States Government mandated the creation of Antimicrobial Stewardship Programs (ASPs) in 2014 with the goal of optimizing patient outcomes while limiting the emergence and spread of antibiotic resistance [5]. Importantly, whenever antibiotics are used to treat an infection, there is a delicate balance between effective antibiotic therapy and disruption of the normal gastrointestinal microbiota, creating opportunities for *Clostridioides difficile* to colonize an already compromised hospitalized individual. Because of its close association with broad-spectrum antibiotic use, *Clostridioides difficile* infection (CDI) is often used as a metric for the effectiveness of ASP interventions. However, studies evaluating the impact of these interventions on CDI rates are most commonly performed within a single center or hospital system and may be underpowered to detect significant changes. Additionally, difficult-to-quantify factors like infection prevention practices and community-acquired CDI (CA-CDI) rates are typically not considered in the analysis of the ASP intervention.

Mathematical models are well-suited to answering research questions regarding the interplay of multiple causal pathways that cannot be experimentally manipulated in practice. A stochastic simulated environment provides the opportunity to experimentally manipulate pertinent variables and identify scenarios under which ASP strategies may feasibly expect to impact CDI rates. Current modeling literature often centers around imported sources of *C. difficile*, such as CA-CDI and asymptomatically

colonized patients [136, 145, 178], varying transition dynamics due to isolating CDI patients [137, 138], and complexities of bundled interventions [146]. Based upon the current understanding of CDI, it is likely that an ASP's influence on hospital CDI rates may only be observed when prescribing of high-risk antibiotics is reduced to a particular magnitude or for a sustained period of time [83].

CDI itself causes nearly half a million illnesses annually in the US. Manifesting as severe diarrheal illness, CDI is associated with prolonged hospitalization and a 50-100% increase in mortality compared to hospitalized individuals without CDI [1]. One in five individuals will have a recurrence in the subsequent 2-8 weeks [2]. Since *C. difficile* spores can persist on surfaces for weeks, CDI can be transmitted person to person directly or via the environment, making the tandem of infection prevention (IP) strategies and antimicrobial stewardship programs (ASP), and specifically how these factors operate within the overall context of the healthcare environment critically important factors in CDI epidemiology.

The magnitude of the risk of CDI that is attributable to antibiotics varies by the specific antibiotic agent, and late-generation cephalosporins, fluoroquinolones, and carbapenems represent high-risk antibiotic classes that are commonly targeted as part of CDI reduction efforts [72-74]. Studies have demonstrated that sustained ASP efforts can successfully reduce these high-risk antibiotics, including up to a 45 percent decrease in cephalosporin use and a 50 percent decrease in fluoroquinolone use [80, 81]. We would expect that these interventions would result in corresponding reductions in HA-CDI rate [83], though that has not always been observed in the literature [6]. The

objective of this study is to create a stochastic model that quantifies the impact of hospital-level antimicrobial stewardship interventions impact on HA-CDI rates given variation in antibiotic use patterns and facility colonization pressure. Our *a priori* hypothesis was that a threshold exists in colonization pressure beyond which ASP interventions would no longer be effective.

5.3 Methods

5.3.1 Model parametrization

We constructed a compartmental model to simulate patients in a 500-bed acute care hospital for a one-year period and included the following mutually exclusive epidemiologic states in relation to *C. difficile*: Unexposed, low risk (U_L); Unexposed, high risk (U_H); Exposed, low risk (E_L); Exposed, high risk (E_H); and diseased (D) (Figure 5.1). "Exposed" refers to exposure to or colonization with *C. difficile*. "High risk" refers to gut microbiome disruption due to intense antibiotic therapy (defined below). "Diseased" refers to symptomatic *C. difficile* infection (CDI). Simulated patients are able to enter and exit the system through any of the states.

We collected our initial parameter values either from previous studies at our institution (Chapter 3 results) [179] or through comprehensive literature review (Table 1). In-hospital exposure to high-risk antibiotic therapy precedes the transition from a low to a high-risk state (U_L to U_H or E_L to E_H). To describe high-risk state based on antibiotic administration, we utilized the antibiotic spectrum index (ASI), which was

established by Gerber et al. and assigns each antibiotic agent a score based on the number of common pathogens against which the agent is active [150]. We identified a threshold of 7 ASI per antibiotic day as a reasonable value to delineate high (≥ 7) and low (< 7) risk individuals. This threshold was derived from our institution's data using a Loess plot (locally weighted scatterplot smoothing) (Appendix Figure 5.1), from which we, through visual inspection, identified an inflection point indicating an amplified increase in HA-CDI risk above 7 ASI per antibiotic day. Additionally, through our group's prior research, we identified a mean of 7 ASI per antibiotic day in our institution's HA-CDI patient population, supporting our choice of threshold [180]. We observed that 20 percent of our inpatient population cross the threshold at our institution on average, and that the median time to crossing the threshold is 2 days (μ, Table 1, Appendix Table 5.1).

We modeled an overall admission rate of 85 admitted adult inpatients per day, reflecting the observed admission rate at our institution. Low risk (U_L and E_L) patients spend an average of 5 days in the hospital, and high risk (U_H and E_H) patients spend an average of 6 days in the hospital. High risk patients experience gut flora recovery after a period of 90 days. High-risk exposed/colonized patients develop symptomatic CDI at a rate 5-times greater than low risk patients. We make the simplifying assumption that any transitions from the exposed/colonized state to the diseased state is incident HA-CDI. After 10 days, CDI patients are either discharged from the hospital (72 percent), return to the high-risk exposed state (25 percent), or died (3 percent). Discharged CDI patients enter a "discharged" state (D_R) for an average of 29 days, where they either are

permanently discharged or re-enter the diseased state as recurrent CDI (12% of discharged CDI patients).

5.3.2 Model implementation

We constructed ordinary differential equations (Appendix Supplement 5.1) to describe the processes of each epidemiological state change. We converted the ordinary differential equations into stochastic processes using Gillespie's Direct method ('GillespieSSA2' package in R) [181, 182]. Epidemiological state transitions are outlined in Table 5.2. We set our initial model state to reflect the proportion of patients admitted of each type (ξ_i, Table 5.1). We ran each simulation for 365 days. We treated the first 90 days of each simulated year as a "wash-in" period to allow the model to equilibrate, then calculated our desired outcomes based on the final 275 days of each modeling period.

5.3.3 Transmission parameter, β

We used Approximate Bayesian Computation (ABC) to fit our *C. difficile* transmission parameter, β [183-185]. ABC is a compartmental modeling technique that draws a candidate parameter from a specified prior distribution, performs a simulation using the drawn value, and accepts the candidate value if the simulated result falls within a specified range (error term) of previously defined target values. For our model, we drew candidate β values from a uniform distribution between 0.00001 and 0.1 and compared the simulated mean number of CDI ("D") patients to a target value for acceptance of 10 and an error term $\varepsilon = 0.2$, indicating that case counts 20 percent above

and below are target count are accepted. We repeated this process 10,000 times, then selected the peak value of the density function of accepted β values as our fitted parameter (Appendix Figure 5.2).

5.3.4 Model calibration and sensitivity analysis

We calibrated our model to achieve a simulated CDI incidence rate that falls between our institution's observed CDI rate (4.4 cases per 10,000 patient days) and national estimates of hospital-onset CDI (8.3 cases per 10,000 patient days) [10]. We also compared prescribing rates and incidence rate ratios for CDI, and to our institution's data [180] and national averages [71]. We performed the following sensitivity analyses: 1) A global sensitivity analysis of μ, β, and ξ_i, where we varied each simultaneously within plausible ranges to determine the relative importance of these parameters while holding the other parameters constant. We selected this set of parameters to evaluate since we believe that changes in HA-CDI incidence due to alterations in antibiotic use (μ) are particularly sensitive to *C. difficile* transmission and colonization pressure (implicit aspects of β) and the types of patients admitted (ξ_i). Other sensitivity analyses include 2) variation of ρ (i.e., are high risk patients exposed to *C. difficile* more quickly than low risk?); 3) variation of γ (i.e., what is the influence of recurrent CDI on the overall system?); 4) variation of τ (i.e., do colonized and infected people contribute similarly to transmission?); and 5) variation of ψ (i.e., what if CDI patients are discharged immediately? What if CDI patients remain in hospital for a long time?). Other technical details of the model follow the MInD-Healthcare model description framework [186], which can be found in Appendix Supplement 5.2.

5.3.5 Applying model to outcomes of interest

We randomly varied μ, β, and ξ_i, according to the specific scenarios outlined in Table 5.3, and Appendix Tables 1 and 2 to determine the impact of hypothetical stewardship interventions on the HA-CDI rate in a variety of plausible hospital settings. We simulated each scenario 1,000 times, generated 95% confidence intervals, and performed Student's t-tests to determine if changes in μ (i.e., simulating successful stewardship) correspond to significant changes in HA-CDI. We also evaluated incremental changes in antibiotic prescribing over time focusing on 30, 60, and 90 days after a hypothetical stewardship intervention by fitting a segmented regression line for each value of μ during each time interval (0 to 30 days, 31 to 60 days, 61 to 90 days).

Model validation

We calculated a pooled incidence rate ratio for 100 simulations comparing the incidence rate for high vs low risk individuals, which was 5.86 (95% confidence interval: 5.53, 6.18). In other words, according to our base model, high risk individuals developed symptomatic CDI at a rate nearly 6-times faster than low risk individuals. This value coheres with reality reasonably well [74], thus providing evidence of our model's validity.

5.4 Results

5.4.1 Baseline model

Running our model simulation 1,000 times using baseline parameterization yields an HA-CDI rate of 7.47 cases per 10,000 patient-days (95% confidence interval: 7.42, 7.52; range: 5.4 to 10.4). On average, there were 96 incident HA-CDI cases per simulated year (range: 70 to 135). Each simulated day, 24.5 patients transitioned into the high-risk state after antibiotic use (range: 23.5 to 25.5). There were 0.4 *C. difficile* transmission events each simulated day (range: 0.28 to 0.57). Simulated CDI mortality was 0.43 deaths per 10,000 patient-days, on average (range: 0 to 1.35). On average, 16 percent of incident CDI cases had a recurrence (range: 3 to 30 percent).

5.4.2 Scenarios

Results of each scenario evaluation are summarized in Table 5.3. The HA-CDI rate was sensitive to changes in context (e.g., higher transmission or more colonized individuals entering the system significantly increased the HA-CDI rate). Reductions in the incidence rate of HA-CDI were significant for the majority of scenarios evaluated. For example, following a 15% reduction in ASI per antibiotic day using our baseline set of parameters, there was a decrease in HA-CDI incidence rate of 0.34 cases per 10,000 patient days (approximately one case per month). Most notably, we observed that the HA-CDI rate did not decrease following successful antimicrobial stewardship intervention in the scenario in which there was high antibiotic use prior to admission (i.e., more patients entering the system directly into U_H or E_H).

Our evaluation of time since hypothetical stewardship interventions of varying effect size is presented in Figure 5.2. In general, reductions in CDI were proportional to

the magnitude of the reduction in μ (the rate of high-risk antibiotic exposure). Peak reductions appear to be around 45 days. According to our fitted segmented regression lines, there were significant reductions in mean CDI count (over 1,000 simulations) for each level of intervention compared to baseline, with reductions between 0.02 and 0.05 cases per day ($p < 0.0001$ for each). Slopes for fitted lines between 31 and 60, and 61 and 90 were not statistically different from zero with the exception of when $\mu = 0.09$ (smallest reduction compared to baseline), there was a slight uptick in mean CDI count between 61 and 90 days after the intervention.

5.4.3 Sensitivity analyses

Results of global sensitivity analysis are visualized in Appendix Figure 5.3. In short, according to standardized estimates, the proportion of colonized individuals (both high- and low-risk) contributed the strongest to increasing the HA-CDI rate. This was followed by antibiotic administration and *C. difficile* transmission in-hospital. The proportion of individuals admitted directly to the disease state did not affect the HA-CDI rate, and higher proportions of uncolonized individuals contributed to lower HA-CDI rates. For the other sensitivity analyses, changes in rho, gamma, and tau changed the HA-CDI rate appropriately. Yet, even at more extreme values, there were not undue influences by these parameters (Appendix Table 5.2).

5.5 Discussion

In this study, we built a stochastic compartmental model to describe the hospital contexts in which reductions in high-risk antibiotic use through antimicrobial stewardship interventions would result in corresponding decreases in hospital-associated *C. difficile* infection incidence rate. We hypothesized that we would be able to detect a threshold where colonization pressure (i.e., the proportion of *C. difficile* colonized or community-acquired CDI patients) would be sufficiently high to render hypothetical stewardship intervention scenarios ineffective in reducing HA-CDI, however we were not able to detect this pattern in our model. In our first six simulation scenarios, there was a direct association between reduction in high-risk antibiotic use and incident HA-CDI, though the proportion colonized with *C. difficile* on admission and in-hospital *C. difficile* transmission had a major impact on the simulated HA-CDI rate. Importantly, we observed that an important threshold of high-risk antibiotic prescribing prior to admission exists and falls between 20 and 25 percent. In this scenario (Scenario 7, Table 5.3), changes in high-risk antibiotic administration do not result in corresponding changes to HA-CDI incidence rate. This simulated scenario could plausibly represent an urban academic referral hospital that receives large proportion of transfer patients in a region with high endemic rates of multidrug resistant organisms and a large proportion of immunocompromised patients, thus leading to regionally higher rates of inpatient prescribing of broader spectrum antimicrobials.

Prior studies have demonstrated that sustained efforts by ASPs can successfully reduce the use of high-risk antibiotics. This includes up to a 45 percent decrease in cephalosporin use and a 50 percent decrease in fluoroquinolone use according to

studies by Feazel et al. and Dingle et al. respectively [80, 81]. While it is understood that ASPs have a positive impact on patient care, the actual metrics to assess these impacts remain poorly understood [86]. For example, a systematic review by Chia et al. reports no reduction in HA-CDI after implementation of stewardship programs, though the authors note that there was a decrease in CDI recurrence [187]. A study by Durant et al. across 44 New York State hospitals demonstrated minor reductions in HA-CDI, though the results were not statistically significant [188]. Additionally, after implementing a prospective audit and feedback ASP, DiDiodato and colleagues report that a ward's CDI count in the previous month was more predictive of risk than overall antibiotic use, suggesting the need to account for environmental sources of CDI [189]. Utilizing our model to demonstrate the specific hospital contexts where HA-CDI rate is responsive to stewardship activities contributes meaningfully to the field by filling an important gap in the literature.

The current body of literature specifically around *C. difficile*/CDI and mathematical modeling shows a great deal of variability in terms of model purpose, structure, and interventions evaluated. A modeling study by McLure et al. aims to describe diverse sources of *C. difficile*, including animals, infants, and asymptomatically colonized adults. The authors report that transmission could plausibly be sustained by infants and asymptomatic carriers, rendering other interventions ineffective [136]. Similarly, our model demonstrates the importance of factors external to the hospital (pre-admission *C. difficile* colonization and/or antibiotic use). Other models simulate isolation of CDI/*C. difficile* colonized patients, suggesting this could be an effective

means to curbing transmission [137, 138]. According to our model, in-hospital transmission significantly affected HA-CDI incidence as well. Two groups have used mathematical models to describe the utility of a potential toxoid vaccine against *C. difficile*, concluding that a vaccine would be effective only if there was a targeted vaccination strategy, interaction between hospitals and other vulnerable populations, and also stress the importance of CDI cases being imported from outside the hospital [139, 140]. Lofgren and colleagues have studied the interaction between *C. difficile* and being in the ICU, concluding that this patient population is in need of particular attention due to increased mortality and hospital lengths of stay [141]. Lanzas et al. suggest through modeling that testing for *C. difficile* on admission to the hospital would reduce new colonization and HA-CDI incidence, suggesting that transmission within the ward alone from patients with CDI cannot sustain new C. difficile colonization and therefore that the admission of colonized patients plays an important role in sustaining transmission in the ward [143]. Chamchod et al. report that infection control strategies are no longer effective in high CA-CDI and high colonization contexts [144]. Agnew et al. describe CDI incidence across European countries and conclude that *C. difficile* transmission dynamics are largely influenced by each national context [134]. Finally, Yakob et al. developed one of the only models that explicitly accounts for microbiome disruption due antibiotic prescribing, though the primary focus of the model was to examine the importance of imported CDI cases [145]. Our model is the first to focus primarily on evaluating stewardship interventions. With the current body of literature around CDI and modeling, an overarching narrative emerges that external *C. difficile*

sources and asymptomatic carriers are of vital importance. This suggests that additional modeling studies are needed to meaningfully inform CDI risk reduction efforts, including those specifically addressing ASP interventions, thus motivating our study.

A 2017 study in Scotland by Lawes et al. examined the effect of a national stewardship intervention aimed at reducing "4C" antibiotics (fluoroquinolones, clindamycin, amoxicillin-clavulanate, and cephalosporins), all high-risk agents for CDI. The intervention successfully reduced 4C antibiotic use in both hospital and ambulatory care settings and reduced CDI incidence in hospitals by 68 percent and 45% in the community [190]. This study illustrates the utility of large-scale stewardship interventions and their impact on CDI. Our model, along with much of the aforementioned literature, highlights the importance of external sources of *C. difficile* and microbiome disruption due to prior high-risk antibiotic use. It is possible that regional interventions would be much more effective than hospital-based interventions in reducing high-risk antibiotics, corresponding to direct reductions in HA-CDI.

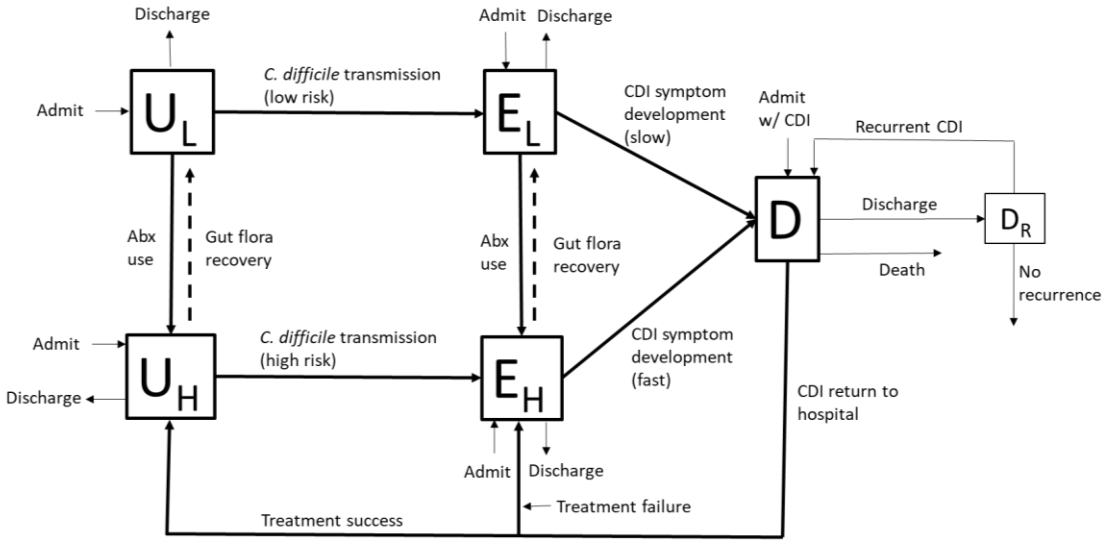
Additionally, our results highlight the importance of stewardship in ambulatory care and lower-risk hospital settings. ASPs often focus on higher-risk settings like large acute care hospitals. Resources are directed to these settings, and CDI is reported to NHSN and is often tied to financial reimbursement [191]. Our model suggests that high-risk antibiotic use prior to admission to the acute care setting renders stewardship in the acute care setting potentially ineffective in reducing HA-CDI. Our study suggests the need for a paradigm shift in stewardship planning and implementation.

Our mathematical modeling study has several limitations. We assume equivalence between exposed and *C. difficile* colonized patients, perhaps oversimplifying the natural history of the organism. More generally, we assume that our model structure is an accurate representation of the hospital environment. While we incorporated ASI into our model to better differentiate high and low-risk patients, ASI was not originally intended to be applied to CDI. Additionally, we did not test the influence of changes to the threshold on our high-risk antibiotic use parameter. This should be done in the future to validate the 7 ASI per antibiotic day threshold. Although our prior research indicates that ASI is useful in explaining the risk attributable to intensity of antibiotic therapy on CDI (Chapter 3), is it possible that another method of differentiating high and low risk patients would be superior.

We developed and implemented a stochastic simulation model that reasonably reflects the epidemiology of HA-CDI in several hospital settings, thus allowing us to evaluate hypothetical antimicrobial stewardship interventions. While we demonstrated the importance of in-hospital transmission, the main modifier of the association between high-risk antibiotic use and HA-CDI was the proportion of admitted patients to the high-risk category due to pre-admission antibiotic use. A high proportion of *C. difficile* colonized patients was a major driver of HA-CDI incidence. Though we were still able to simulate reductions following stewardship, the absolute reduction in cases was small and may not be noticeable as part of a stewardship program. It is important to take pre-admission factors into consideration when using HA-CDI incidence rate as a

metric for stewardship success. In some settings, it is likely that other outcome-based metrics for stewardship evaluation should be employed.

Figure 5.1. Compartmental model design



U_L, unexposed, low risk; U_H, unexposed, high risk; E_L, exposed/colonized, low risk; E_H, exposed/colonized, high risk; D, diseased (symptomatic *C. difficile* infection); D_R, disease with possibility of recurrence; CDI, *C. difficile* infection; Abx, antibiotics

Table 5.1. Epidemiological model symbology and parameterization

Symbol	Description	Value	Source
ξ_i	Proportion of admitted patients of type *i*	U_L: 0.787 E_L: 0.045 U_H: 0.15 E_H: 0.015 D: 0.003	[21, 136, 192], OHSU
α	Overall admission rate	85 patients per day	OHSU
θ_i	Discharge rate for non-CDI patient of type *i*	High risk (H): 0.167 per day Low risk (L): 0.2 per day	OHSU
κ_i	Rate of symptomatic CDI development in patient of type *i*	E_L: 0.004 per day E_H: 0.02 per day	[145, 193]
ι	Rate of discharged CDI patients potentially developing recurrence	0.034 per day	OHSU
γ	Proportion of discharged patients developing recurrence	0.12	OHSU
ω	Probability of death in CDI patients	0.03	[91, 145]
ψ	Rate of treatment and/or discharge in CDI patients	0.10 per day	OHSU
χ	Proportion of CDI patients discharged	0.72	OHSU
λ	Rate of gut flora recovery	0.011 per day	[145]
β	Hazard of exposure to C. difficile from environment contact/HCW/person-to-person	0.009454 per day	ABC Fitted
ϕ	Proportion of CDI patients remaining in hospital and returning to high-risk state	0.25	OHSU
μ	Rate of crossing ASI per antibiotic day threshold	0.1 per day	OHSU
ζ	CDI treatment failure	0.1	[194]
τ	Increase in transmission rate by infected patients vs colonized	1.33	[144]
ρ	Increase in transmission rate for high-risk patients vs low	1.5	Sensitivity analysis

OHSU, Oregon Health & Science University electronic health record data – all adult inpatients from January 1, 2018 to March 23, 2020; ABC, Approximate Bayesian Computation

Table 5.2. Epidemiological state transitions of the stochastic model

Process	Category	Propensity (∂t)	State change
High risk antibiotic treatment	Unexposed	μU_L	U_L-1, U_H+1
	Exposed	μE_L	E_L-1, E_H+1
Gut flora recovery	Unexposed	λU_H	U_L-1, U_H+1
	Exposed	λE_H	E_L-1, E_H+1
***C. difficile* exposure**	Low risk	$\beta U_L \left(\frac{E_H + E_L + \tau \mathrm{D}}{N}\right)$	U_L-1, E_L+1
	High risk	$\beta \rho U_H \left(\frac{E_H + E_L + \tau \mathrm{D}}{N}\right)$	U_H-1, E_H+1
CDI symptom development	Low risk	$\kappa_L E_L$	E_L-1, D+1
	High risk	$\kappa_H E_H$	E_H-1, D+1
Post CDI return to:	Exposed	$\zeta \phi \psi D$	D-1, E_H+1
	Unexposed	$(1-\zeta) \phi \psi D$	D-1, U_H+1
Discharged from D (CDI)		$\chi \psi D$	D-1, D_R+1
CDI recurrence		$\gamma \iota D_R$	D_R-1, D+1
Admission to:	U_L	$\alpha \xi_{U_L}$	U_L+1
	U_H	$\alpha \xi_{U_H}$	U_H+1
	E_L	$\alpha \xi_{E_L}$	E_L+1
	E_H	$\alpha \xi_{E_H}$	E_H+1
	D	$\alpha \xi_D$	D+1
Death		$\omega \psi D$	D-1
Discharged from:	U_L	$\theta_L U_L$	U_L-1
	U_H	$\theta_H U_H$	U_H-1
	E_L	$\theta_L E_L$	EL-1
	E_H	$\theta_H E_H$	E_H-1

CDI, *Clostridioides difficile* infection

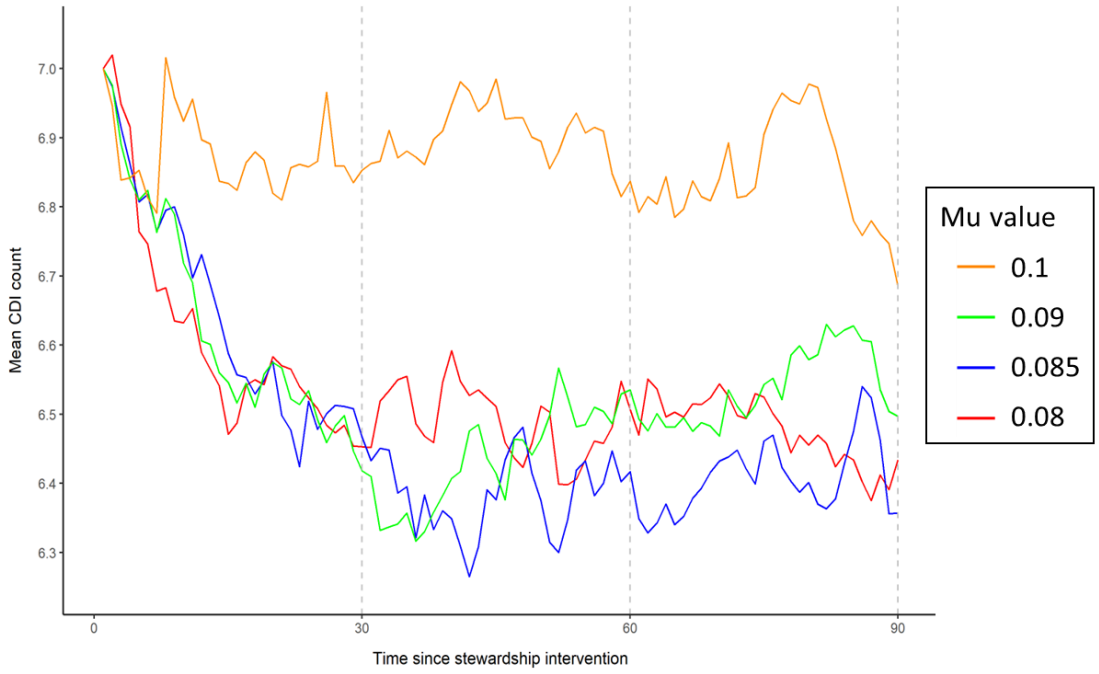
Table 5.3. Hypothetical antimicrobial stewardship interventions in varying hospital contexts

Scenario	*C. difficile* transmission in hospital	Colonized on admission	High-risk antibiotics prior to admission	Reduction in ASI per antibiotic day after hypothetical stewardship interventions	HA-CDI rate per 10,000 patient-days and 95% confidence intervals	p-value
	Hospital Characteristics					
1 - Suburban, community hospital with low *C. difficile* community and hospital prevalence and high proportion of direct admissions	Low	Low	Low	None	7.17 (7.13, 7.22)	REF
				5%	7.06 (7.01, 7.10)	<0.01
				10%	6.97 (6.93, 7.02)	<0.01
				15%	6.87 (6.82, 6.91)	<0.01
2 - Model calibration setting based on OHSU primary data	Medium	Low	Low	None	7.47 (7.42, 7.52)	REF
				5%	7.28 (7.23, 7.32)	<0.01
				10%	7.18 (7.14, 7.23)	<0.01
				15%	7.13 (7.08, 7.18)	<0.01
3 - Urban academic referral hospital in high comorbidity patient setting and moderate *C. difficile* community and hospital prevalence	Medium	Medium	Low	None	11.71 (11.65, 11.77)	REF
				5%	11.41 (11.35, 11.47)	<0.01
				10%	11.32 (11.26, 11.38)	<0.01
				15%	11.16 (11.10, 11.22)	<0.01
4 - Scenario 3 high *C. difficile* prevalence geographic region	Medium	High	Low	None	18.66 (18.59, 18.74)	REF
				5%	18.37 (18.28, 18.44)	<0.01
				10%	18.11 (18.04, 18.18)	<0.01
				15%	18.01 (17.94, 18.08)	<0.01
5 - Scenario 4 plus Hospital-onset CDI SIR above 1.0 (due to large number of ICU beds, longer LOS, etc.) [157]	High	High	Low	None	19.98 (19.91, 20.06)	REF
				5%	19.57 (19.50, 19.65)	<0.01
				10%	19.35 (19.28, 19.43)	<0.01
				15%	19.17 (19.09, 19.24)	<0.01
6 - Urban academic referral hospital with moderate rates of multidrug resistant organisms leading to higher inpatient prescribing geographic region	Medium	Low	Medium	None	9.26 (9.20, 9.31)	REF
				5%	9.16 (9.10, 9.21)	<0.01
				10%	9.08 (9.03, 9.14)	<0.01
				15%	9.01 (8.96, 9.06)	<0.01
7 - Scenario 6 with high rates of multidrug resistant organisms and immunocompromised inpatients leading to high inpatient prescribing in region.	Medium	Low	High	None	11.83 (11.77, 11.89)	REF
				5%	11.77 (11.72, 11.83)	NS
				10%	11.84 (11.78, 11.91)	NS
				15%	11.78 (11.72, 11.83)	NS

Abbreviations: NS, not significant at a 0.05 level; SIR, Standardized Infection Ratio; LOS, hospital length of stay

Note: P-values generated from Student's t-test compared to "None" category in the same scenario. The model was calibrated under scenario 2 (medium transmission, low colonized on admission, low level of high-risk antibiotic use prior to admission). Each HA-CDI rate estimate is the mean of 1,000 simulations.

Figure 5.2. Simulated reductions in mean CDI count following hypothetical antibiotic stewardship interventions compared to baseline, 1000 simulations



Note: Mu represents the rate at which patients move from low-risk to high-risk states due to intense antibiotic therapy. Smaller values of mu indicate more prudent antibiotic administration.

Chapter 5 Appendices

Appendix Table 5.1. High-risk antibiotic administration parameter derivation

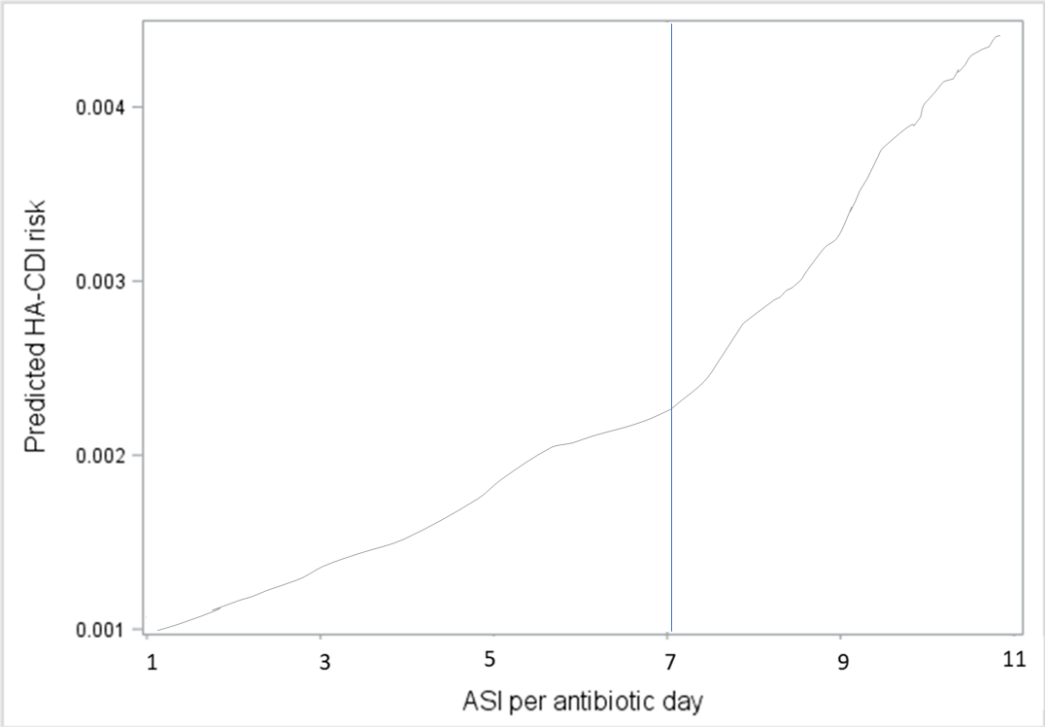
Reduction in mean ASI per antibiotic day	Proportion of patients crossing high-risk threshold	Corresponding μ value
None	0.2	0.1
5%	0.18	0.09
10%	0.17	0.085
15%	0.16	0.08

Note: The model was calibrated using a prescribing rate of 3.8 ASI per antibiotic day. Smaller μ values represent a slower transition rate from low to high risk.

Appendix Table 5.2. Derivation of context parameter categories

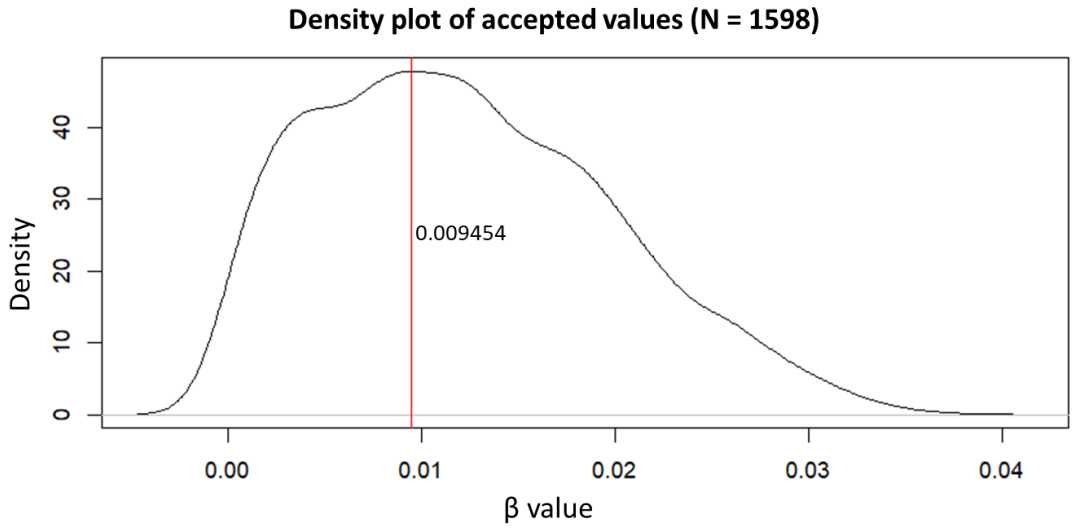
Parameter/context	Level	Value	Source
Transmission within the hospital, β	Low	0.00613	Fitted lower quartile
	Medium	0.00945	Fitted median
	High	0.01761	Fitted upper quartile
Colonized/CDI upon admission, $\xi_{E_L}, \xi_{E_H}, \xi_D$	Low	6%	[136, 195]
	Medium	10%	North American pooled estimate [21]
	High	15%	[20]
High risk antibiotics prior to admission ξ_{U_H}, ξ_{E_H}	Low	16.5%	OHSU data
	Medium	20%	[196]
	High	25%	[154, 197, 198]

Appendix Figure 5.1 Loess plot of ASI per antibiotic day and predicted HA-CDI risk (inflection point at 7 ASI per antibiotic day)



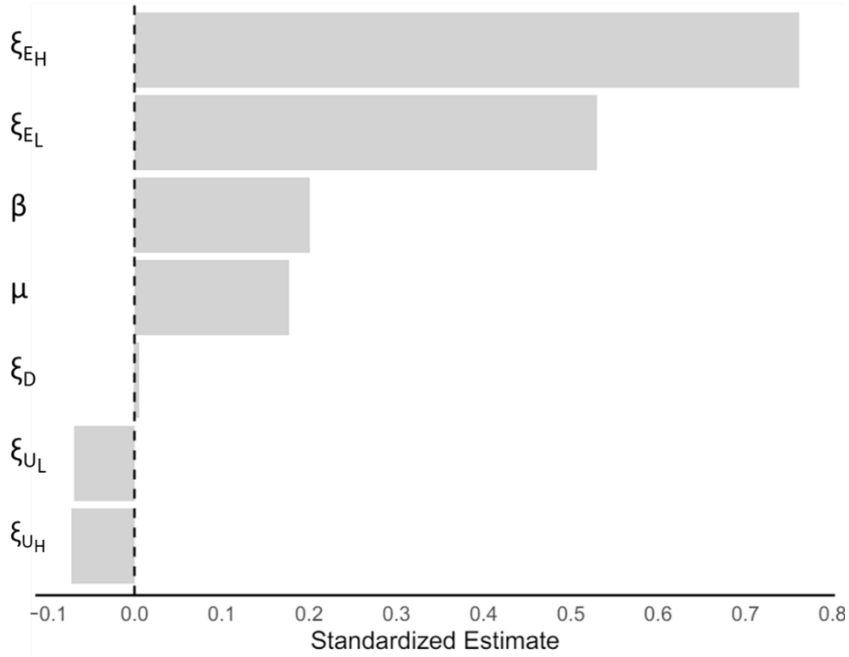
Note: Inflection point (vertical line) identified through visual inspection

Appendix Figure 5.2 Density function plot for accepted beta values from Approximate Bayesian Computation (ε = 0.2)



Note: Red line represents the peak value of distribution of values. Figure generated in R-studio.

Appendix Figure 5.3. Global sensitivity of selected parameters (10,000) simulation



Note: Each individual parameter varied randomly. We then fit a line using multivariable regression model to generate standardized coefficient estimates.

Appendix Table 5.3. Results of sensitivity analyses

Parameter	Range	Coefficient*	P-value	Notes
ρ	1 – 10	0.43	<0.0001	The HA-CDI rate is 10.9 per 10,000 patient days at the highest decile of ρ
γ	0 – 1	0.13	<0.0001	The HA-CDI rate is 7.6 per 10,000 patient days when γ > 0.95 (nearly everyone recurs)
τ	1 – 5	0.02	<0.0001	Even when infected individuals influence transmission at a rate 5x greater than colonized, changes in HA-CDI are minimal
ψ	0.047 – 1.5	-0.03	0.08	Faster discharge slightly reduces HA-CDI rate, though changes could be due to chance

*Coefficients represent change in HA-CDI rate per one unit change in the parameter value according to a simple linear regression model

5.6 Supplementary Material for Chapter 5

Appendix Supplement 5.1. Ordinary differential equations used to construct stochastic model

$$\frac{dU_L}{dt} = \alpha\xi_{U_L} + \lambda U_H - \mu U_L - \theta_L U_L - \beta U_L \frac{(E_H + E_L)}{N} - \beta\tau U_L \frac{D}{N}$$

$$\frac{dU_H}{dt} = \alpha\xi_{U_H} + \mu U_L + (1-\zeta)\phi\psi D - \lambda U_H - \theta_H U_H - \beta\rho U_H \frac{(E_H + E_L)}{N} - \beta\rho\tau U_H \frac{D}{N}$$

$$\frac{dE_L}{dt} = \alpha\xi_{E_L} + \lambda E_H + \beta U_L \frac{(E_H + E_L)}{N} + \beta\tau U_L \frac{D}{N} - \mu E_L - \theta_L E_L - \kappa_L E_L$$

$$\frac{dE_H}{dt} = \alpha\xi_{E_H} + \mu E_L + \zeta\phi\psi D + \beta\rho U_H \frac{(E_H + E_L)}{N} + \beta\rho\tau U_H \frac{D}{N} - \lambda E_H - \theta_H E_H - \kappa_H E_H$$

$$\frac{dD}{dt} = \alpha\xi_D + \gamma\iota D_R + \kappa_L E_L + \kappa_H E_H - \omega\psi D - \chi\psi D - \phi\psi D$$

$$\frac{dD_R}{dt} = \chi\psi D - \iota D_R$$

Appendix Supplement 5.2: MInD-Healthcare framework

Purpose and scope:

Purpose: The purpose of this model is to examine the contexts in which successful antimicrobial stewardship will lead to a corresponding decrease in healthcare-associated *Clostridioides difficile* infection (HA-CDI). Many of our model parameters were estimated from EHR data from our institution. The rest of our parameters are based on empirical literature.

Scope: A 500-bed academic medical center in the US.

Entities, state variables, and scales:

Entities: Patients

State variables: Patients are classified as Unexposed, Exposed/Colonized, or Diseased. Unexposed and Exposed/Colonized individuals are further separated into high or low risk categories. Diseased individuals who are discharged from the hospital go into a holding state where they can either have a recurrence or be discharged permanently.

Scale: A 500-bed academic medical center simulated for one year.

Initialization: In the initial state of the model (time = 0), there were 379 unexposed, low risk individuals; 90 unexposed, high-risk individuals; 20 exposed, low risk individuals; 10 exposed, high-risk individuals; and 1 diseased individual. There were zero individuals in the post-disease holding state. This initial state reflects the admission rate for each type

of patient. We also used a 90-day burn-in period to ensure that the model reached stochastic equilibrium.

Process overview and scheduling:

Tables 1 and 2 in the main manuscript describe the modeling processes in detail. We simulated the model using Gillespie's Direct Method [181], which randomly selects event occurrence based on predetermined rates. There is no defined scheduling structure.

Input data:

The model does not directly use any external input data, though we estimated some of our parameters using data from OHSU's Pharmacy Research Repository [152, 199].

Agent interactions and organism transmission:

Interactions: Interactions between patients are density dependent.

Transmission: Disease and Exposed/Colonized patients can transmit *C. difficile* to any unexposed patient, though at differing rates. We did not directly model environmental or healthcare worker transmission, but this process is implied in our fitted transmission parameter.

Stochasticity:

This model represents a fully stochastic process. Times and even recurrence is fully stochastic.

Submodels: We did not implement any submodels.

Model verification, calibration, and validation:

Verification: We verified our model code through careful inspection and careful review by our group's modeling expert (ETL). We also performed extreme value tests, where we set several of our parameters to implausibly high or low values and had our model return equally implausible results.

Calibration and validation: We calibrated our model to produce and average HA-CDI incidence rate that fell between our institution's (OHSU) observed HA-CDI rate and national average estimates [10]. We fit our *C. difficile* transmission (β) parameter using Approximate Bayesian Computation [184], drawing 10,000 candidate values from a uniform distribution bound by 0.00001 and 0.1, compared to a target value of a mean of 10 diseased individuals (plus or minus 2). We validated our model by generating several summary measures, such as average incidence rate ratios comparing high and low risk patients, average prescribing rates, and *C. difficile* infection recurrence rate to ensure that these results were reasonably coherent with reality.

Chapter 6: Synthesis of research

6.1 Overview and restatement of hypothesis

The overall objective of this dissertation research was to evaluate the specific set of conditions required to observe meaningful reductions in hospital-associated *C. difficile* infection rate after successful antimicrobial stewardship initiatives (i.e., achieving reductions in unnecessary, broader-spectrum than necessary, or longer duration than necessary antibiotics/antibiotic courses). While HA-CDI can be an informative patient-centered outcome when evaluating ASPs due to its close association with broad-spectrum antibiotic therapy, empirical evidence in the literature is lacking. This uncertainty is, in no small part, due to the variation in the magnitude of risk from antibiotics, CDI's complex causal factors, and reliance on ASP-specific evaluations that are underpowered, single-center or single-system studies. I set out to address these issues with my dissertation project.

In my first specific aim (Chapter 3), I built a marginal model using a Generalized Estimating Equations approach to achieve a more granular understanding of HA-CDI risk from antibiotics. To accomplish this, I utilized the antibiotic spectrum index (ASI), which had not previously been applied to CDI as an outcome [150, 151, 200]. I hypothesized that ASI would accurately describe the intensity of antibiotic therapy and estimate the risk of HA-CDI from antibiotics after controlling for other known CDI risk factors, and that ASI would describe HA-CDI risk from antibiotics more accurately than the more commonly used days of therapy (DOT).

For my second specific aim (Chapter 4), I performed an interrupted time series analysis to achieve a better understanding of how drastic changes to the healthcare context in response to the COVID-19 pandemic altered HA-CDI epidemiology. Using the pandemic as a natural experiment presents us with a rare opportunity to reflect on context-based risk CDI risk factors. I hypothesized that we would see an initial increase in HA-CDI incidence at the pandemic's onset due to increases in broad-spectrum antibiotic prescribing, followed by a gradual return to pre-pandemic levels.

Finally, my third specific aim (Chapter 5) involved building and testing a stochastic, mathematical model so I could experimentally simulate the hospital environment to evaluate specifically how successful stewardship interventions impact HA-CDI incidence across a variety of simulated contexts. My hypothesis was that we would see significant reductions in HA-CDI incidence after successful hypothetical stewardship, but not in contexts with a high proportion of *C. difficile* colonized or community-acquired CDI admitted patients.

6.2 Summary of findings

In Aim 1, patient-level ASI points per antibiotic day was strongly associated with HA-CDI risk after controlling for twelve additional known CDI risk factors. The full model fit the data well and outperformed DOT in its ability to describe HA-CDI risk. We selected variables for our model using VanderWeele's disjunctive cause criterion [155]. Therefore, we included five non-significant covariates in our model. Significant CDI risk factors included time-at risk, number of comorbid conditions, proton pump inhibitor or

H2-receptor antagonist use, nasogastric tube placement, gastrointestinal procedures, chemotherapy, and *C. difficile* colonization pressure. In addition to relative risks, we translated our model coefficients into absolute risk difference and number needed to harm values, thus rendering our results more clinically applicable. Because of HA-CDI's rarity, the absolute risk differences were small, and number needed to harm values large.

In Aim 2, we observed significant increases in both the frequency and intensity of antibiotic use (i.e., more antibiotic days and higher ASI per antibiotic day) during the COVID-19 pandemic era than the 24 months prior, along with increases in average patient age, time at-risk, and number of comorbid conditions. It should be noted, however, that the magnitude of the ASI per antibiotic day increase was modest (0.9 additional ASI per antibiotic day). It is possible that ASI per antibiotic day underestimates the intensity of prescribing at the group level due to the presence of antibiotic days in the denominator (e.g., increases in antibiotic days decreases the variable's value). Despite the apparent increases in risk factors, we did not detect significant changes in HA-CDI at the pandemic's onset and over the course of the first year, adjusting for average ASI per antibiotic day, colonization pressure, and comorbidity burden. When adding a second interruption point starting at the pandemic's second year, there was a slight increase in HA-CDI incidence according to our adjusted segmented regression model. According to Aim 1, an increase of 1 ASI per antibiotic day corresponds to a NNH of 5,400 (Appendix Table 3.2). It is possible that it took until the second year of the pandemic for the additional risk conferred by the ASI

increase to manifest as additional HA-CDI cases. Colonization pressure was highly influential in our model in that removing this variable substantially decreased model fit (R^2 = 0.29 vs 0.60). Additionally, *C. difficile* testing did not change on a per-encounter basis during the pandemic, mitigating concerns of bias due to misclassification of cases. Importantly, *C. difficile* colonization pressure declined steadily throughout the pandemic. In a *post hoc* analysis, we confirmed this was partially due to a decrease in patient movement throughout the hospital.

My Aim 3 model builds on results from the first two aims. Based on Aim 1 results, we identified a threshold of 7 ASI per antibiotic day to differentiate high and low-risk patients. Aim 2 highlighted the importance of colonization pressure, and while we did not explicitly code this onto the model, we carefully selected our *C. difficile* in-hospital transmission parameter (which implicitly includes colonization pressure) to boost our model's accuracy. The model was able to reasonably simulate HA-CDI epidemiology in a hospital setting similar to OHSU. Importantly, incremental decreases in high-risk antibiotic administration after hypothetical stewardship interventions were followed by decreases in HA-CDI incidence in most simulated scenarios. However, when the proportion of admitted patients had previous high-risk antibiotic exposure was high (greater than 20%), the incidence rate of HA-CDI no longer changed after simulated stewardship interventions reduced high-risk antibiotic administration. In-hospital transmission and the proportion of patients colonized with *C. difficile* on admission highly influenced HA-CDI, though these did not render stewardship ineffective in reducing HA-CDI.

We can relate our Aim 3 modeling results to Aim 1 using our estimated, adjusted NNH values. Using our baseline model parameters, each 5 percent decrease in high-risk antibiotic administration (population mean ASI per antibiotic day) prevents approximately 250 individuals from crossing ASI per antibiotic day threshold during the simulation period. This decrease corresponds to, on average, the prevention of one HA-CDI case. According to Aim 1 predictive margin results (Appendix Table 3.2), a NNH of 250 corresponds to an average decrease of 12 ASI per antibiotic day. While the threshold is set at 7 ASI per antibiotic day, it is possible that the model is overestimating the effect of stewardship on CDI reductions. However, we cannot directly measure the simulated ASI per antibiotic day for high-risk individuals in the model. According to our Aim 1 data, among those with 7 or greater ASI per antibiotic day, the mean ASI per antibiotic day is 10.6. Furthermore, while the model was calibrated mostly using our institution's data, our simulated HA-CDI outcome was higher than what we observed in Aim 1 (Chapter 3). Therefore, changes in antibiotic administration could have a different impact on HA-CDI in the simulated setting than what we observed. It is possible that an ASI per antibiotic day of 12 is a plausible value for the high-risk patient mean.

A few key themes have emerged from these specific aims. First, ASI's ability to explain HA-CDI risk is promising. I utilized ASI per antibiotic day as a measure of intensity of antibiotic therapy for all three specific aims, and the measure performed well across three different study designs. Broad-spectrum antibiotic therapy is still a key risk factor for CDI. ASI gives us a tool to understand this risk more granularly and helps preserve statistical power enabling us to control for other important risk factors. A second theme

is that *C. difficile* colonization pressure is of utmost importance to CDI epidemiology. Colonization pressure was an influential independent risk factor in our Aim 1 model. In Aim 2, decreases in colonization pressure likely played a role in mitigating what should have been in increase in risk due to rising antibiotic use. Additionally, colonization pressure greatly improved our segmented regression model's fit. In Aim 3, while colonization pressure was not explicitly included in the model, in-hospital *C. difficile* transmission was a major driver of simulated HA-CDI cases. Finally, all three aims have demonstrated the importance of context when evaluating the association between antibiotics and HA-CDI, and therefore, HA-CDI's utility as a metric for stewardship success. In addition to inpatient antibiotic use, several other risk factors were highly significant in our Aim 1 model. In Aim 2, the rapidly changing context brought about by the pandemic appears to have rendered the association between antibiotics and HA-CDI of lesser import. Finally, our Aim 3 model demonstrated how changing contexts alone can greatly influence HA-CDI incidence and render stewardship ineffective in reducing HA-CDI if the proportion of patients with disrupted microbiomes is too high. CDI epidemiology is complicated, and patient, facility, and regional contexts must be considered.

6.3 Overall limitations and remaining questions

This dissertation research does have some important limitations. Overall, the HA-CDI burden at our institution is low compared to the national average (4.4 vs 8.3 cases per 10,000 patient-days) [10], which presents concerns about our research's generalizability. For this reason, we calibrated our Aim 3 model to simulate an HA-CDI

incidence that fell between our institution and the national average. Additionally, ASI was not specifically developed to be applied for CDI. For example, clindamycin carries a 4-fold increase in risk over sulfamethoxazole-trimethoprim, though both agents have as ASI of 4. For this reason, it is likely that ASI has more of an application at the population level rather than as a tool for individual-level CDI prediction (i.e., *average* reductions in population level ASI will typically reduce HA-CDI incidence depending on the context). The specific tailoring of ASI to CDI is likely a question worth addressing.

A specific limitation of our Aim 2 interrupted time series design is that our capacity for causal inference is limited due to its quasi-experimental nature. Additionally, due to aggregating data over 30-day periods and the aforementioned low HA-CDI incidence, we had some time intervals with very few or even zero cases. This presents an important limitation in statistical power to detect HA-CDI trends over time. Finally, we did not have data on infection prevention activities or PPE use, so we can only hypothesize that these played the most significant role in keeping HA-CDI rate consistent despite the marked increase in risk factors.

A clear limitation of mathematical modeling involves the simplifying assumptions we must make to implement models for practical use. There remains the risk that we have not correctly specified any number of parameters or the model structure itself so that the model does not accurately represent the environment we are trying to simulate. We also fit our in-hospital transmission parameter to the data instead of explicitly modeling transmission events, so we are unable to explain the role of any single transmission component (e.g., colonization pressure, hand hygiene,

environmental exposure). Finally, we incorporated ASI into our model to better differentiate high and low-risk patients. Though our prior research indicates that ASI is useful in explaining the risk attributable to intensity of antibiotic therapy on CDI, is it possible that another method of differentiating high and low risk patients would be superior.

6.4 Significance and contributions of research

This dissertation makes a significant contribution to the literature in the evaluation of antibiotic stewardship along with general CDI prevention. I have incorporated ASI into three different study designs to more accurately quantify the varying magnitude of risk of CDI from antibiotics. Incorporating ASI into a regression model allows us to adjust for multiple CDI risk factors without needing the large sample size of a multi-center study. Additionally, incorporating the ASI threshold into a stochastic compartmental model reflects reality more accurately than treating antibiotic exposure as a binary (yes/no) variable, as has been the case in prior modeling studies.

This dissertation also highlights the importance of *C. difficile* colonization pressure as an independent risk factor for CDI. Colonization pressure was a highly influential variable in my first two aims, and part of a highly influential (transmission) parameter in my third aim. We were able to calculate colonization pressure using our institution's comprehensive, longitudinal patient location data. An observed decrease in colonization pressure due to less patient movement could explain why HA-CDI incidence did not increase during the pandemic. To my knowledge, this has not been demonstrated elsewhere. Overall, colonization pressure appears to be an accurate

proxy for the likelihood of *C. difficile* exposure and should be accounted for when possible.

Finally, our Aim 3 model itself represents a significant contribution to the field. Our model is the first, to my knowledge, to specifically address antimicrobial stewardship in a variety of contexts. Additionally, by defining a threshold using ASI per antibiotic day, we believe we have more accurately simulated reality (i.e., hospitalized patients can receive less intense antibiotic therapy and remain low risk for CDI). This model can be adapted to reflect a specific healthcare facility's set of characteristics, allowing for researchers, clinicians, infection preventionists and stewardship personnel to understand when HA-CDI can be used as a metric for stewardship success.

Ultimately, the question of if and when HA-CDI is a quality metric for stewardship success remains difficult to assess. We believe that it is a useful metric in the context of community or suburban hospitals with a low comorbidity burden and few transfer patients. This would limit the proportion of individuals admitted with already disrupted microbiomes, thus rendering HA-CDI a useful metric for stewardship. In contexts with higher comorbidity burdens and greater proportion of transfer patients, HA-CDI might not be the best metric for stewardship and thus, another outcome measure is needed. Stewardship personnel should consider these specific contextual factors when evaluating stewardship interventions.

6.5 Future directions

While this dissertation has addressed several gaps in the literature, CDI prevention and HA-CDI as a metric for stewardship success remains a rich topic for further research. As is true with any single-center study (Aims 1 and 2), expanding this research to other sites would solidify our conclusions and ensure our research's generalizability. Data availability and data sharing are crucial components to this work.

We have also demonstrated ASI's utility in describing HA-CDI risk from antibiotics at the population level. A clear expanded application of this work involves utilizing ASI for individual-level CDI prediction. While this likely would require altering the ASI calculation specifically for CDI (e.g., accounting for gut bioavailability and minimum inhibitory concentration (MIC) values across specific antibiotic agents), this could have a major impact on HA-CDI prevention.

Finally, our Aim 3 model can be adapted for research, stewardship, and quality improvement across a variety of healthcare settings. For example, stewardship personnel can re-calibrate the model to fit their facility and determine the expected response in HA-CDI incidence after a stewardship intervention. We have demonstrated that some contexts would not expect to see HA-CDI reductions. While this does not imply that the stewardship initiative failed, it does mean that HA-CDI is not a useful metric in that scenario. Knowing when to tether or untether ASPs and CDI is of vital importance, as the emergence and spread of antimicrobial resistance remains an urgent threat [78]. The model can also be adapted to better understand community-acquired and recurrent CDI. Finally, explicitly parameterizing different aspects of in-hospital *C. difficile* transmission is another promising area of study that will allow us to better

understand CDI's complex epidemiology. Antimicrobial stewardship, CDI prevention, and prevention of the emergence and spread of drug resistant organisms are inextricably linked. I believe that this dissertation has addressed many key issues and that it will inform additional research and clinical efforts.

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