INTEGRATING THE PATIENT SHARING NETWORK AMONG HEALTHCARE FACILITIES INTO THE CONTAINMENT OF CARBAPENEM-RESISTANT ENTEROBACTERALES IN TENNESSEE

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Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

In partial fulfillment of the requirements

For the degree of

DOCTOR OF PHILOSOPHY

In

Epidemiology

August 12, 2022

Nashville, Tennessee

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To my husband, Herdi

And my mother and father and their big dreams for me

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SPECIFIC AIMS

Antibiotic-resistant organisms (AROs) cause 2.8 million infections and 35,000 deaths annually in the United States. Among these organisms are carbapenem-resistant Enterobacterales (CRE), a group of bacteria resistant to nearly all antibiotics, restricting treatment to more toxic or less effective antibiotics. CRE is attributed to 13,100 cases among hospitalized patients and 1,100 deaths annually. CRE that produce carbapenemase, an enzyme that breaks down carbapenem antibiotics carbapenemase-producing CRE, also known as CP-CRE. These bacteria contain genes in their plasmid and spread resistance to neighboring bacteria.

CRE and other AROs primarily cause healthcare-associated infections. Previous healthcare exposure is the primary risk factor for acquiring CRE, and patient movement across healthcare facilities has been shown as a means of transmission (1,2). In recent years, more research on the role of patient sharing networks in transmissions of antibiotic-resistant organisms has been conducted to assess the patient sharing network constructed from the general patient population (3).

The objective of this dissertation was to analyze the impact of incorporating the patient sharing network in the multi-facility coordinated containment efforts. We first constructed the patient sharing network from the statewide hospital discharge data to achieve this objective. We utilized information from this network to help epidemiologists prioritize downstream facilities to contain antibiotic-resistant organisms. We linked these administrative data with CRE surveillance data to gather risk factors, healthcare utilization, and outcomes of CRE cases. Mandatory CRE reporting in TN allowed the construction of a statewide cohort of CRE cases, and mandatory isolate submission provided information on carbapenemase production status.

We organized the dissertation into three specific aims:

Specific Aim 1: To assess patient characteristics associated with hospital re-admissions among CRE patients. We analyzed a retrospective cohort of patients reported with CRE infections in Tennessee and analyzed the patient characteristics associated with their re-hospitalization within 12 months.

Specific Aim 2: To evaluate the association between hospitals' patient sharing network (PSN) metrics and hospital-level CRE prevalence. We used the results from the first study aim to create a CRE surrogate population from the general patient population. Using a negative binomial model, we hypothesized that hospital-level centrality measures, specifically generalized indegree, were independently associated with facility-level CRE cases per 1,000 patient days.

Specific Aim 3: To model the impact of a coordinated multi-facility containment strategy on the regional CRE prevalence after three years. We simulated a mathematical model to estimate the impact of incorporating a coordinated containment on the prevalence of CRE in Tennessee after three years.

Published mathematical models developed by CDC suggested that a coordinated prevention approach involving connected healthcare facilities and public health would reduce the acquisitions of multidrug-resistant organisms by 76% in three years. Our study identified the network structure and assessed the role of the patient sharing network for this coordinated approach, progressing the research to a more actionable approach for public health interventions by health authorities.

CHAPTER 1

Background

1.1 Epidemiology of Carbapenem-Resistant Enterobacterales (CRE)

The invention of antimicrobial agents to treat infections was one of the most important medical discoveries in the 20th century. Since antibiotics are available, infectious diseases that were historically fatal for humans became treatable, and physicians can now perform surgical procedures long considered risky due to potential post-surgical infections (4). However, since its discovery, antibiotics have been prescribed to patients with viral or other non-bacterial etiology like asthma, allergy, bronchitis, and influenza (5). Bacteria exposed to antibiotics may die, but some could evolve to survive by developing resistance mechanisms. Inappropriate antibiotic use is the primary contributor to the emergence and rise of antimicrobial resistance (6,7).

The resistance of bacteria to one or more groups of antibiotics can lead to untreatable infections, resulting in severe morbidity and death. According to a report published by the Centers for Disease Control and Prevention (CDC) in 2019, antibiotic resistance causes 2.8 million infections and 35,000 deaths in the United States annually (7). The World Health Organization (WHO) and the CDC warned about the coming of the post-antibiotic era in which common treatable infections would be fatal again for humans (7,8).

Carbapenem-resistant Enterobacterales (CRE) is one of the most concerning antimicrobial-resistant organisms (AROs). CRE are gram-negative bacteria that developed resistance to carbapenems, a group of broad-spectrum β-lactam antibiotics. Clinical laboratories routinely perform susceptibility testing for four carbapenem antibiotics approved for clinical use in the US, specifically meropenem, imipenem, doripenem, and ertapenem(9). Because of the rapid emergence of resistance to more commonly prescribed cephalosporin antibiotics, clinicians generally prescribe carbapenems as the last resort antimicrobial agents for gram-negative bacterial infections with resistance to other agents(10). For these reasons, the CDC listed CRE as an urgent threat, the highest classification among AROs (7,11,12).

Enterobacterales can develop resistance to β-lactam antibiotics through cellular membrane-mediated changes or by producing β-lactam hydrolyzing enzymes (6,13). The cellular-mediated

mechanisms, including efflux pumps or porin mutations, are less commonly found (13). Enterobacterales primarily develop resistance through the production of β-lactam hydrolyzing enzymes, the most concerning being carbapenemases. CRE carry the genes that encode the cellular instructions to produce carbapenemase on mobile genetic elements called plasmids instead of the cell nucleus. These plasmids can move between cells and transfer the genes they carry to different genera. The plasmid-mediated resistance mechanism found among CRE means that resistance to carbapenems can be passed vertically to their descendants and laterally to neighboring bacteria (6,13,14). This potential for transmission of resistance capabilities makes Carbapenemase-producing CRE (CP-CRE) a priority for containment (7,15).

In the United States, the rise in CRE prevalence in the last two decades was primarily attributed to the spread of CP-CRE, which produce *Klebsiella pneumoniae* Carbapenemase (KPC) (3,12,16). KPC is one of the many carbapenemases among CP-CRE. This resistance mechanism was initially detected among *K. pneumoniae*, but other genera of Enterobacterales have since produced KPC after acquiring the plasmid-mediated genes. Furthermore, CRE patients in the United States have been increasingly infected or colonized by other carbapenemases more commonly found outside of the United States, including the New Delhi Metallo-β-lactamase (NDM), Verona Integron-encoded Metallo-β-lactamase (VIM), Oxacillinase-48-type carbapenemases (OXA-48), and the Imipenemase (IMP) Metallo-β-lactamase. Most of these patients had a history of international travel or domestic healthcare exposure (7,11). A systematic review of CRE epidemiology in 2015 estimated CRE incidence to be 0.3–2.93 infections per 100,000 patient-years in the United States (12). The clinical studies on CRE variably reported the mortality rate among CRE infected or colonized patients as 14-day (17–19), 90-day (20), and 1-year (15,16), or in-hospital mortality (4,17). The mortality rates ranged from 6.6% in a study in seven metropolitan areas of the states participating as CDC Emerging Infections Program (EIP) sites in 2015 (11) to as high as 71% among liver transplant recipients and 82.4% in an intensive care unit in Chicago (20).

CRE are commonly identified as healthcare-associated infections (HAIs) and disproportionately affect the young, elderly, and patients with underlying chronic illnesses (25). These patients may have a compromised immune response and encounter more acute care hospitals and long-term care settings for rehabilitation or skilled nursing care (7,11,12). As a collaborative regional effort to understand the burden of multi-drug resistant organisms (MDROs) in healthcare

facilities, the SHIELD Orange County project screened patients for CRE and other MDROs, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus spp*. (VRE), extended-spectrum β-lactamase-producing organisms (ESBL) among patients treated in 38 healthcare facilities. They found MDRO colonization among 65% of Long-Term Care Facilities (LTCFs) residents and 80% of Long-Term Acute Care Hospitals (LTACHs) patients.

LTCFs, specifically skilled nursing facilities, nursing homes, and assisted living facilities, care for frail and older residents and are especially vulnerable to MDROs. Increasingly complex medical procedures devices, communal living settings, and dependence on healthcare workers increase the risk of MDRO infections among LTCF residents (26). Additionally, CRE isolates reported from EIP sites are mainly collected from patients hospitalized the year prior, and most were later discharged to LTCFs or LTACHs (11). Both these findings highlight the importance of these long-term facilities in CRE transmission and containment efforts.

Based on the known CRE epidemiology in literature, the regional spread of CRE is likely to be influenced by the bacterial host factors that increase transmissibility, the containment efforts and infection control practices, the frequency of re-admissions of infectious patients, and the movements of CRE patients across healthcare facilities. One of the factors that influence transmissibility is the duration of CRE colonization. The following sections of this chapter address the body of research on CRE colonization duration, the frequency of re-admission of patients colonized or infected with CRE during their initial hospitalization, and the association between patient sharing networks and CRE incidence. Appendix 3 lists the search keywords and strategies in PubMed, Embase, and Web of Science with specific study questions relevant to these topics in this chapter.

1.2 Duration of CRE Colonization

CRE are found in clinical settings as an infection or colonization based on the type of clinical culture collected from a patient. CRE colonization, sometimes referred to as CRE carriage, occurs when the organism is found in the body without causing any disease symptoms (3,7,27). Patients may be colonized, most commonly in their gastrointestinal tract, after or without previously being infected with CRE. Thus, rectal swabs are the most common way to screen for CRE colonization.

CRE-colonized patients may unknowingly carry and transmit the pathogens to others during their subsequent admission to a healthcare facility either through contact with contaminated surfaces or through the hands or clothing of healthcare workers (28–30). They are also at increased risk of developing CRE infection in the future (31,32).

Studies examining the duration of CRE colonization reported that patients might be colonized at variable durations without decolonization therapy. Prolonged CRE colonization was associated with more frequent hospital re-admissions and extended hospitalizations since initial CRE detection, comorbid conditions like diabetes mellitus, and concurrent *Clostridiodes difficile* infection (CDI) (33,34). National and international health agencies recommend no specific decolonization therapy for CRE colonization. Nevertheless, the CDC recommends bathing patients with 2% liquid chlorhexidine gluconate (CHG) or 2% CHG-impregnated wipes for patients in high-risk settings or LTCF residents regardless of CRE colonization status (35). CHG bathing, particularly at concentrations 128 µg/ml is, can reduce KPC colonization on the patients' skin, according to a study conducted in an LTCF in Chicago, where CRE is endemic (36). A few clinical trials have also evaluated the efficacy of fecal microbiota transfer (FMT) (37,38) or selective digestive decolonization therapy using oral antibiotics like oral Colistin, Gentamicin, or Polymyxin E (38,39). Based on the existing guidelines and findings in the literature, patients are unlikely to receive decolonization therapy after being diagnosed with CRE colonization. Therefore, understanding CRE colonization duration is essential to establish the appropriate interval between hospital stays to construct a patient-sharing network.

This review includes the findings of 13 clinical studies published in the last 15 years that evaluated the duration of CRE colonization or reported frequency of CRE colonization. Additionally, a meta-analysis of Bar-Yoseph *et al.* included studies published in 2011-2013 and estimated that without decolonization treatment, 35.2% (95% Confidence Interval [CI]: 28.2–42.9%) of patients were persistently colonized after 12 months (40). Table 1.1 summarizes the clinical studies that reported the proportion of CRE colonization at one month or more since initial CRE detection. Only one study was conducted in LTACHs (41); most were conducted in tertiary acute care hospitals. The data on CRE colonization status and duration in these studies were gathered from one of these sources; reports of active surveillance screening often conducted after an outbreak, abstraction of medical charts, or findings from the control group of a decolonization

therapy clinical trial. Many studies reported the colonization of CRE as a composite with other MDROs, including VRE, Cephalosporin-Resistant Enterobacterales, and ESBL-producing Enterobacterales, as one compound outcome. Only the reports of CRE colonization were included in this review if the studies reported them separately.

The screening protocols varied across studies. CRE screening in clinical trials or as part of active surveillance during a facility-wide containment effort used fixed screening follow-up of hospitalized patients for at least a portion of their study period. Isolates collected after hospital discharge are usually obtained on outpatient visits based on a recommended follow-up schedule. Spontaneous decolonization or clearance was also variably defined; as one negative culture in four studies (38,41–43) or two or three negative cultures. Some studies that described decolonization as two negative cultures also warranted the isolates to be collected at least 48 hours (34) or seven days apart (44,45); two studies did not define specific intervals between the two negative isolates (33,44). The strictest definition of clearance was used in studies that used data from active screening programs with three negative cultures at least 48 hours (46) and one week apart (47).

The clinical studies in this review reported the proportion of persistent colonization rate at variable periods, the longest being two years in one study with only six subjects remaining to provide samples (46). Colonization lasting more than three years is possible, as documented among a minority of patients (46). CRE colonization persisted in 17-33% of patients after 12 months of follow-up in four studies (42,43,45). Table 1.1 lists the studies that reported the proportion of colonized patients observed from specific sample collection points or the Kaplan-Meier survival curve estimates. A study conducted on 21 patients in Singapore (48) that only predicted a 1.5% chance of colonization after 12 months from a Bayesian model was excluded from the review. The proportion of observed colonization was 71%-83% after one month (38,41), and 33%-93% in 90 days (33,34,47,49,50). A few observational studies and pooled meta-analyses included in this review reported the median colonization duration of 22-295 days (41,43,48,49) and the mean of 324-387 days (41,43).

The colonization duration observed in these studies should be interpreted with some considerations based on the study populations. This review characterizes the study population to include incident events if they only reported colonization of newly identified CRE-colonized patients during the study period and prevalent events if they reported known carriers or previously

known carriers before the follow-up or the index hospitalization. In four studies, all patients who tested positive for CRE from a facility-wide active surveillance screening program were included and analyzed as a homogenous group. However, they did not examine when patients began to be colonized and treat all patients as one population. The patient population comprised a mix of newly and previously CRE-colonized patients (33,34,42,47). Oren *et al.* and Davido *et al.* included and discriminated between the incident and prevalent events in their studies. In the few studies that examined incident events, the researchers collected isolates from the patients before they acquired CRE, and colonization duration was measured since their first positive CRE isolates. They reported the median colonization duration before study enrollment for prevalent events of 54-140 days (38,44). None of the studies strictly included incident events. Thus, the colonization duration reported in this review is likely to underestimate the natural colonization duration of CRE.

Some studies assessed the bacterial and patient factors associated with prolonged colonization. Kim *et al.* found that *K. pneumonia* isolates and concurrent CDI infection are associated with longer colonization duration (47). Kim *et al.* and Davido *et al.* examined the difference in colonization duration between resistance mechanisms but did not find OXA-48-like carbapenemase, the most common carbapenemase in their studies, to be associated with prolonged colonization. Several comorbidities were associated with longer colonization duration, including hematologic malignancies or solid tumors (51), diabetes mellitus (43), or a composite of comorbidities calculated as high Deyo-Charlson Comorbidity Index (DCCI) (33). Additionally, longer hospitalization duration (34,49), re-admission after initial hospital discharge (34,42,43,46), older age (43,51), low functional status (33,43,51), positive clinical culture (34,42,47), and discharge to LTCF (33,43) were also risk factors of longer colonization.

There are a few notable observations that may influence the observed colonization duration. Firstly, hospital surveillance data and medical records were valuable resources for analyzing a CRE colonization duration with large sample size. The patients in these retrospective studies provided samples at outpatient visits or on re-admissions instead of pre-determined follow-up time points. Therefore, the proportion of colonized patients had to be estimated using the Kaplan-Meier survival method. In the studies conducted as retrospective cohorts, the decolonization rate can be influenced by the facility's screening protocol and infection prevention bundles during the study period. Secondly, many studies reported a substantial loss of follow-up,

especially after three months. Patients with more complex medical conditions probably provided more follow-up data and samples, which signals a potential selection bias that could overestimate proportions of persistent colonization. For example, Haverkate *et al.*'s study used the non-adherence to the existing screening protocol to gather data on colonization duration. Causes of the loss to follow-up reported in the studies include death, not having follow-up outpatient visits, or not being re-admitted to the same hospital during the study period.

1.2.1 Pooled Analysis and Forest Plot

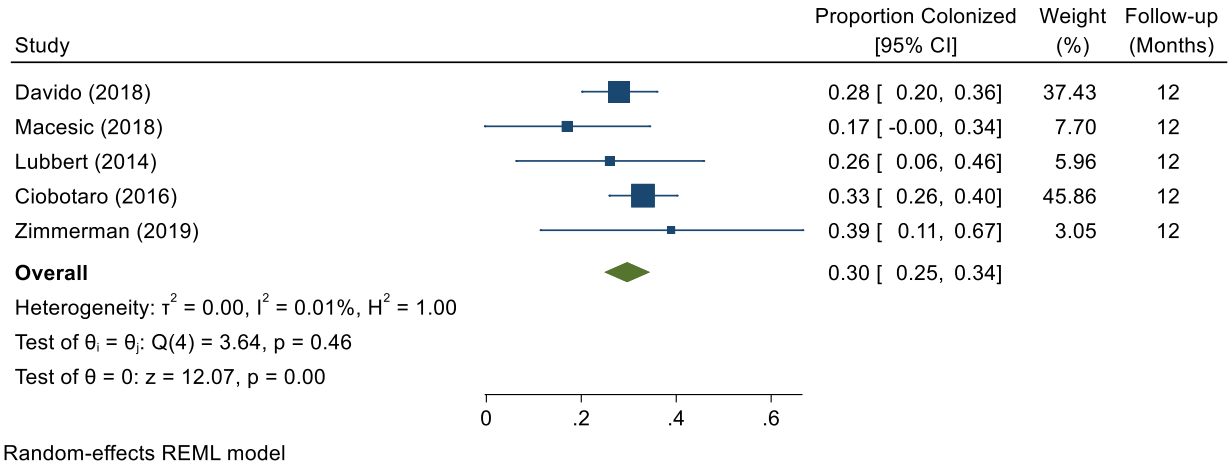
The individual proportions of patients with persistent CRE colonization were assessed to determine whether they could be pooled into a single estimate. First, the findings from CRE colonization studies were grouped into two groups; (1) estimates from 12 months and (2) estimates from less than 12 months of follow-up. One study can report a proportion of persistent colonization both 12 months and under 12 months of follow-up; we included these estimates but grouped them separately. Studies that reported multiple colonization proportions under 12 months, e.g., three months and six months, were included using their longest follow-up point. The CRE colonization rates from less than three months were excluded from the pooled analysis and forest plots because the short follow-up did not represent persistent colonization.

We generated forest plots summarizing the findings from the studies using the meta-analysis menu in Stata 16. Estimates were pooled using the random-effects maximum likelihood estimator. Additionally, findings of persistent colonization were reported in addition to the 12-month estimate. However, these estimates were beyond the period of interest in this dissertation and had few subjects. Oren *et al.*'s study was also excluded because they were reported from a select population of high-risk individuals in ICU units. The proportion of colonized patients in this study may skew the pooled estimates and contribute to the heterogeneity of the findings.

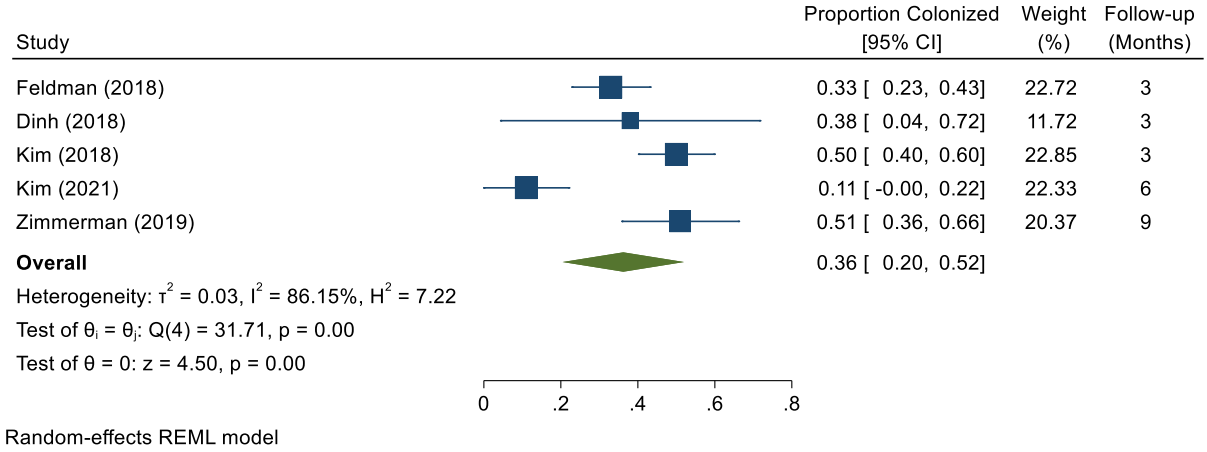
The forest plot of persistent CRE colonization at 12 months of follow-up is shown in Figure 1.1.a. The pooled estimate of the proportion of patients colonized with CRE at 12 months was 0.30 (95% CI: 0.25–0.34), suggesting a substantial proportion of patients were still estimated to be colonized at 12 months. Five studies reported the proportion of patients still colonized at 12 months since hospital discharge. Ciobotaro and Davido et al.'s study contributed the highest weight to the pooled estimate among these studies. The studies were relatively homogeneous ($I^2 = 0.01\%$), and

Egger's test did now show evidence of small-study bias (p=0.46). However, it should be noted that Egger's test is underpowered to detect bias when the number of studies is small.

The forest plot of persistent CRE colonization proportion among studies with less than 12 months of follow-up is shown in Figure 1.1.b. These studies are highly heterogeneous (I^2 = 86.15%), and Egger's tests showed evidence that the estimates may suffer from small-study bias ($p < 0.001$). These findings suggested that the estimates from individual studies should not be pooled into a single estimate due to their heterogeneity. In conclusion, the published literature on the natural history of CRE colonization showed reported durations and proportions of persistent colonization over time. Nevertheless, the findings from these studies imply that despite the decreasing proportion of persistent colonization over time, a non-negligible proportion of patients still harbor CRE and pose the risk of transmission at their subsequent healthcare encounters at 12 months following their initial infection or colonization.



(a) at 12 months of follow-up



(b) Less than 12 months of Follow-up

Figure 1.1 Forest plot of CRE colonization survival estimates of studies

Table 1.1 Summary of Studies Reporting the Proportion of Persistent CRE Colonization

Author, Year	Incident or Prevalent Events and Patient population	Screening Protocol Frequency, Samples, and Follow-up Details	Decolonization (n; negative interval)	n	Reported Time Points (n at risk)	% Colonized
Saidel-Odes, 2012 (39)	Prevalent; patients with oropharyngeal or rectal *K. pneumonia* CRE identified within the week of study randomization in a decontamination clinical trial	Day 0 (initial diagnosis), day 9, week 2, week 4, week 6 for rectal cultures	1	20	6 weeks	41.5%
Oren, 2013 (51)	Incident and prevalent; patients with positive CRE rectal surveillance cultures randomized into a control group due to refusal of consent or having isolates that are resistant to oral antibiotics treatment	On admission to the hospital, from high-risk patients and routinely once weekly in selected wards. Median follow-up 14 days (20-737). Median swabs 6 (range 2-16)	3; undefined	102	3 months	93%
Lubbert, 2014 (46)	Incident and prevalent; Patients infected or colonized with CP- CRE with KPC-producing *K. Pneumonia* during a hospital outbreak and implemented screening	Variable; at each re-admission, or fixed; at outpatient follow-up at 1,3,6, 12, and 24 months since discharge	3; 48 hours	84	12 months (n=19) 24 months (n=6)	26% 17%
Haverkate, 2016 (41)	Prevalent; LTACHs patients with incident CRE colonization with KPC with at least one follow-up	On each admission and every other week during hospital stays until first positive isolate. Study data on colonization duration is based on screening protocol non-adherence. Median isolates provided = 2 (IQR 2-2)	1	137	28 days (n=137)	83%
Huttner, 2019 (38)	Prevalent; Non-immunocompromised adults in with prevalent ESBL-E and/or CP-CRE as a control group for FMT.	At five time points, at baseline (day of enrollment), on day 8-15, 16-28, 35-48, and 150-210 since enrollment.	1	16; 5/16 CP-CRE	35-48 days (n=16)	71%
Davido, 2018 (49)	31 Prevalent and 94 incident events ***; CRE (73%) or VRE (27%)	Fixed; Weekly screening. VRE and CRE colonization are not reported *separately*	2; 1 week	125	1 year (n=18)	28%

	patients readmitted after previous CRE colonization					
Dinh, 2018 (44)	Prevalent; Clinical trial of immunocompetent patients with CRE or VRE colonization receiving FMT	Fixed; Day 7, 14, 21, and monthly for 3 months regardless of decolonization status	2; 7 days or 1 month after the 1st month	8	3 months (n=8)	38%
Feldman, 2018 (33)	Incident and prevalent; Carriers of KPC *K. pneumonia* from surveillance cultures who were not critically ill and provided consent for prospective cohort follow-up	Fixed; baseline at first screening/clinical culture, before the initial discharge of hospitalization at study enrollment, at 2 weeks, 1, 2, and 3 months since discharge. If persistent positive at month 2 and 3 months, additional testing	2; variable	225	3 months (n=83)	33%
Kim, 2018 (34) [Busan, Korea]	Incident and prevalent; Patients identified as CRE carriers during active surveillance by rectal swabs or clinical cultures with culture data for three months or more	Variable; at re-admission, weekly in ICU or after initial positive culture, and recommended at least monthly post-discharge*	2; 48 hours	100	3 months (n=100)	50%
Kim, 2021 (47) [Anyang, Korea]	Incident and prevalent; patients identified as CP-CRE carriers via rectal swabs or clinical culture during weekly active surveillance in a hospital ICU	Fixed; during hospitalization: weekly until three consecutive negatives; Monthly recommendations for outpatients. Only a proportion of patients followed at 6 months	3; 1 week	514	3 months (n=188) 6 months (n=31)	44% 11%
Macesic, 2018 (45)	Prevalent and incident; Patients undergoing liver transplantation who had CRE, VRE, of Ceph-RE colonization	Fixed; at pretransplant enrollment, transplant hospitalization, and months 2,3,6,9, 12 post-transplants. Median 8 (IQR 4-12) samples per patient	2; >1 week	25	12 months (n=18)	17%
Zimmerman, 2019 (42)	Incident and prevalent; Patients with CRE positive culture from rectal swab screening or clinical culture with the first culture during the study period and at least one follow-up culture	Variable; during re-admission or as part of follow up in outpatient clinic. N with 1 follow-up = 41; 2 follow-up=19, ≥3 follow-up=37; Mean= 2.5	1 or more without subsequent negative; variable	97	3 months (n=82) 6 months (n=58) 9 months (n=42) 12 months (n=30)	78% 65% 51% 39%

Ciobotaro, 2016 (43)	Incident and prevalent; All patients identified as CRE carriers during screening or clinically who were re-admitted after initial hospitalization where CRE is identified	Variable; Once every re-admission for patients with previous CRE colonization, and clinically at clinicians discretions. Median isolate or person at risk at each time point not reported	1	168	12 months 24 months	33% 15%

*Data from 6 and 12 months excluded from table because of low follow-up denominator.

**All statistics reported were combined between CP-CRE and ESBL-E.

***Prevalent cases are considered as patients who were known to be colonized before hospitalization. Incident cases were discovered to be colonized at admission.

Abbreviations: CRE, Carbapenem-Resistant Enterobacterales; LTACHs, Long-Term Acute Care Facilities; CP-CRE, Carbapenem-Producing CRE; KPC, Klebsiella pneumonia Carbapenemase; FMT, Fecal microbiota transfer; n, number of subjects evaluated without pharmaceutical intervention in clinical trial arms, or all patients assessed in observational studies.

Note: The two Kim *et al.*'s studies were conducted in two different hospitals and patient populations.

1.3 Re-admissions of CRE Patients

Patients hospitalized for non-infectious causes may develop hospital-onset infections during their stay. Patients may be exposed to pathogens through the hands of healthcare workers, direct contact with other patients, or the hospital environment. Hospital-onset infection is a risk factor for future hospital re-admissions (52–54). Patients are likely to have caught MDRO infections during hospitalizations as HAIs, and they are usually older or have comorbidities that require frequent healthcare encounters and hospitalizations (28,55). MDROs may colonize a patient for months and causes future infection and possibly transmission during subsequent healthcare encounters, including those at a different facility than the discharging one. CRE colonization combined with frequent re-admissions poses a challenge to facility infection preventionists in preventing infections and stopping further transmissions to other patients or healthcare workers within the healthcare facility catchment (15). Patients with a cerebrovascular accident or stroke, for example, may acquire CRE colonization during their index hospitalization, be discharged to an LTACH, and eventually discharged into nursing homes or other types of LTCFs before hopefully returning to a home environment. Each transfer may introduce CRE to each admitting facility while still colonized, putting other patients or residents at risk.

Patient-sharing networks are visualized from network datasets that specify the number of transferred patients from one facility to another. These datasets have been constructed by aggregating the number of re-admissions of the general patient population through direct transfers or indirect transfers, representing patient re-admission to another hospital after a period of intervening stay in the community (56). To accurately represent the re-admissions that pose a risk of interfacility transmissions, indirect transfers should be defined using the typical duration of community stays of the patients colonized with the MDRO of interest. The knowledge about the frequency of re-admissions and median length of community stays between hospitalizations can provide valuable insight into the magnitude of risk posed by previously infected or colonized CRE patients to subsequent admitting facilities.

Most published studies examining re-admission rates of previously CRE-colonized or infected patients were conducted in single tertiary academic medical centers (18,29,30,34,57,58). All studies reported only re-admissions after hospital discharge within their hospitals. The re-

admission rates of CRE patients between two healthcare facilities are relevant to the transmission risks in the region. Tabak *et al.* (28) included most patients and gathered data from 78 healthcare settings in 2013-2015 from a de-identified hospital research database obtained by a third-party provider, BD Insights Research Database. However, their study included all carbapenem non-susceptible organisms instead of using the standardized CRE case definition from the Council of State and Territorial Epidemiologists (CSTE) in 2015 (59). Therefore, non Enterobacterales genera like *Pseudomonas* and *Acinetobacter* were included in their study. Additionally, they only described the re-admission rates of patients within each hospital, thus unable to provide information about interfacility patient transfers.

The findings from studies with fixed follow-up suggest that the re-admission rates of CRE patients increase as the follow-up period extends. Two studies reported 30-day re-admission rates of previously infected or colonized patients of 16.9%-32% (28,30), two had 90-day re-admission rates of 61%-72% (18,34), and one had one-year re-admission of 60% (29). Two studies also performed a survival analysis of re-admission during a variable follow-up period exceeding 12 months, including a 60.3% re-admission rate within 712 days (57). A small study of eight patients reported 62.5% re-admission rates within 20 months (58). Previously infected or colonized CRE patients were discharged to LTCFs 39% and 77% of the time in two studies (34). Table 2 summarizes the findings of these studies.

The lack of knowledge on re-admissions of CRE patients to other facilities highlighted the gap in understanding the implications of admitting CRE patients to other healthcare facilities that may have less infection prevention capacity as tertiary centers. Their findings suggest that the known re-admission rates may underestimate re-admissions of CRE patients to all types of facilities in the population. The first aim of this dissertation described re-admission rates by matching patients to their admissions in a statewide database of hospital admissions over 12 months or more of follow-up.

Table 1.2 Summary of Studies Reporting the Proportion of Re-admissions of CRE Patients

Author, Year	Study Setting, Country (Year)	Included Organisms	Specific CP Studied	Patient Population	N	Follow-up	% Re-admission
Ny, 2015 (30)	Single Tertiary Center, United States	Carbapenem-Resistant K. pneumoniae	No	Hospitalized adults with pneumonia or UTI	48	Fixed, 30 days	32.0%
Tabak, 2020 (28)	78 healthcare sites, United States	Carbapenem non-susceptible organisms: *P.aeruginosa* (57.5 - 82.2%), other gram negatives (5.9 - 7.4%), polymicrobial (0-15.1%)	No	Hospitalized adults with ≥1 Carbapenem non-susceptible Respiratory isolates	6,830	Fixed, 30 days	16.9%
Neuner, 2011 (18)	Single Tertiary Center, United States	Carbapenem-Resistant K. pneumoniae	No	Adults with Carbapenem-Resistant K. pneumoniae bloodstream infections	25	Fixed, 90 days	72.0%
Kim, 2018 (34)	Single Tertiary Center, South Korea	KPC CP-CRE;	Yes, KPC	CRE carriers from the rectal or clinical culture with at least three months of follow-up	100	Fixed, 90 days	61.0%
Burnham, 2018 (29)	Single Tertiary Center, United States	All Enterobacterales with ESBL: Enterobacterales (29%) Others (71%)	No	All patients with any MDRO isolates, including ESBL-producing Enterobacterales	1,008	Fixed, 365 days	60.0%
Ciobotaro, 2016 (43)	Single university-affiliated hospital, United States	CRE	No	All patients who were identified as CRE carriers at index hospitalization with at least one re-admission during a 7-year study period	168	Fixed, 30 days	43.5%

Evain, 2019 (57)	Single Tertiary Center, France	CP-CRE	Yes, OXA-48	Colonized patients during an outbreak period	189	Variable, 0- 712 days	60.3%
Vigara, 2020 (58)	Single Tertiary Center, Spain	CP-CRE	Yes, KPC	Renal transplant recipient with CP-CRE infection	8	Variable, 0- 20 months	62.5%

Abbreviations: CRE, Carbapenem-Resistant Entrobacterales, CP-CRE, Carbapenemase-producing CRE; KPC, Klebsiella pneumonia carbapenemase; OXA-48, Oxacilinnase-48-type carbapenemase; UTI, urinary tract infections; MDRO, multidrug-resistant organism; ESBL, extended-spectrum β-lactamase; P.aeruginosa, *Pseudomonas aeruginosa*

1.4 Coordinated Multi-Facility Containment Approach

CRE is associated with poor patient outcomes in healthcare settings. CP-CRE pose an additional challenge because they carry the genes encoding their resistance mechanism in mobile genetic elements capable of transfer to neighboring bacteria. They spread the carbapenem resistance to other bacteria with pre-existing resistance to other antibiotics, potentially creating a highly drug-resistant "superbug" (60). WHO and CDC advocated incorporating the One Health perspective to reduce ARO reservoirs and community prevalence. Within this perspective, the environment, human, and animal health are interconnected. For example, actions to reduce antibiotics in the community should include limiting ARO-contaminated water reservoirs for agricultural or human water sources and reducing mass medication of farm animals with antibiotics among the proposed environmental interventions (61).

Antibiotic stewardship programs are also essential to reduce antimicrobial resistance in clinical settings. The primary driver of resistance is inappropriate prescribing of antibiotics to treat non-bacterial infections. Antibiotic stewardship is an effort to quantify and improve antibiotics prescriptions in clinical settings. Pharmacists work with doctors and other prescribers in healthcare facilities to optimize the selection of antibiotics, assess treatment appropriateness with the results of diagnostic tests, and ensure the shortest duration of therapy that could effectively rid the infection.

Furthermore, the development of new antimicrobial agents or vaccines can reduce the impact of antimicrobial resistance on human health (62,63). Effective vaccines can prevent ARO infections and the consequential need for antimicrobial therapy, which eventually could reduce the emergence of resistance. Therefore, vaccines could contribute in a significant way to reduce antimicrobial resistance. A few trials are underway for vaccines against pathogens commonly implicated as MDROs, including *K. pneumonia, Pseudomonas aueruginosa,* and *Staphylococcus aureus*. However, vaccine developments take time, averaging between 10 to 20 years. Most of these trials are still in the preclinical phase or early clinical stages in 2021. The new vaccine platforms, combined with a change of interactions between manufacturers and the government, successfully accelerated the vaccine development process, as seen in the vaccine against the SARS-Cov-2 virus. The experience from the vaccine development, especially the public-private

collaboration like seen during the pandemic, could guide future vaccine development for MDROs partnership, including when conducting trials in low and middle-income countries where the burden of antimicrobial resistance is significant.

Nevertheless, novel resistance threats emerge more quickly than the invention of new antimicrobial therapies or changes brought by stewardships or environmental interventions. Thus, efforts to contain the transmission of MDROs are currently the most feasible intervention with immediate impact to reduce the spread of antimicrobial resistance in healthcare settings(7).

In 2017, the CDC published the interim guidance for the public health response to contain novel or targeted MDROs. The CDC guideline classified containment efforts into three response tiers based on the organisms and resistance mechanism, with tier one requiring the most aggressive approach for organisms posing the highest threat. This guideline considers the most common carbapenemase in the United States, CRE, that produces KPC as tier 3 organisms because they have been identified frequently in the region without being endemic. Less common carbapenemases are classified as tier-2 organisms. In all response tiers, identifying targeted MDROs in the index facility initiates a prompt initial notification and involvement of the health departments and prompt implementation of appropriate infection control measures. Public health laboratories capable of molecular detection of resistance mechanisms can assist the rapid detection of MDRO threats. Additionally, infection preventionists should collaborate with public health entities to investigate the patient healthcare exposures before and after the positive culture, and contact investigation ensues with varying levels according to the response tiers.

When a facility identified a targeted MDRO, the containment efforts are often only focused on their facility. Measures such as hand hygiene, separation of infected or colonized patients into cohorts to avoid interactions with non-infected patients, and consistent use of contact precautions during care for colonized or infected patients have been documented to reduce transmission at the facility level effectively (22,64,65). However, CRE transmissions at the regional level cannot be eliminated only by facility-level interventions because patients can remain colonized for months. Each healthcare encounter of colonized patients can introduce CRE in the next facility. Thus, additional interventions involving state or local public health agencies and healthcare facilities that often share patients are necessary to reduce regional CRE incidence.

The CDC guidance also recommends the coordination of the response among healthcare facilities. The coordination should include facilities that treated the patients before or after the case was identified, and facilities commonly share patients with the index facility. The assessment of transmission through surveillance and screening of patients may extend beyond the index facilities. Therefore, it is crucial to understand the patient-sharing network and the flow of patient transfers between healthcare facilities to maximize the effectiveness of the containment strategy.

The literature on containment efforts has mainly described the bundled infection control strategy within a healthcare facility that has successfully eradicated or reduced transmission of MDRO outbreaks. These bundled measures most commonly include reinforcement of environmental cleaning (65), hand hygiene campaigns (66–70), contact precautions (65,71), cohorting patients with dedicated nursing staff (39,65,72–74), and active surveillance or screening at the index facility when recommended by public health (75–78). Additionally, some hospitals reported installing disinfection devices on sinks using heat and electromagnetic vibration (75) and replacing sink drains to reduce the number of incident CRE cases. Hospital infection preventionists pursued these measures when they suspect environmental reservoir to be the culprit of a persistent outbreak (75,79). Among the reports of CRE outbreaks associated with the water drainage system, eliminating the horizontal drainage system was reported to eradicate a CRE outbreak (71).

Our literature search on successful outbreak containment reports utilizing a multi-facility coordination approach yielded few results. Israel, a small country with ~14,000 hospital beds, reported a successful CRE outbreak containment with national-level coordination after local measures failed (80). Although no literature specifically cited successful outbreak containment using a patient-sharing network, the Tennessee Department of Health has successfully managed outbreaks and reports of novel resistance mechanisms by adhering to the CDC interim guidance (personal communication). CRE is a reportable condition in Tennessee, and clinical laboratories are mandated to send CRE isolates to the State Public Health Laboratory (SPHL) for further carbapenemase testing. If carbapenemase production was detected or the gene that confers carbapenemase production is identified, TDH epidemiologists assign the case as a CP-CRE and contact the facility to treat the patient to gather healthcare exposures or healthcare contacts information. Screening of healthcare contacts, patients treated within the same room or facility, may be conducted if the index patient was not placed in contact precautions before they were found

to have CRE. TDH epidemiologists and infection preventionists also guide the facility in its containment efforts. If they suspect that interfacility transmission has occurred or is imminent, TDH epidemiologists also facilitate the coordination between healthcare facilities and SPHL to contain CRE transmission.

The CDC guidance recommends active screening of transferred patients to identify CRE colonization among patients in a healthcare facility after the initial detection. A team in Rush University Medical Center in Chicago also reported an implemented protocol to screen transferred patients. Their findings showed that active screening is feasible and could detect CRE in 3.3% of screened patients. However, CRE colonization status was inconsistently reported in the patient transfer forms. The lack of interfacility communication on patients' CRE colonization status may indicate that many cases may be missed in other settings that did not implement active screening(81). Improvements in interfacility communication and screening could potentially prevent regional transmissions and outbreaks of CRE.

The case for multi-facility coordination is even strengthened by the initial findings of the SHIELD Orange County Project. This collaborative regional effort uses a patient-sharing network to recruit facilities with high patient sharing to control MDRO spread through MDRO colonization screening. Their active screening results showed that recruited facilities have a high burden of MDRO colonization, which demonstrated the potential of leveraging the patient-sharing network data on reducing transmission at the regional level (82).

1.5 Association Between Patient-sharing network and MDRO Epidemiology

Genetic linkages between CRE cultures collected in facilities linked by patients admitted to multiple facilities further support the theory that direct or indirect patient transfer is a means of regional spread of CRE (7). Aggressive containment strategies and hospital infection prevention programs have shown success, as evidenced by a 27% reduction in hospital-acquired infections from 2011-2017 (7). However, a collaborative approach between facilities may be able to increase the effectiveness of the containment further. Mathematical models have shown that collaboration between facilities that share patients can reduce CRE acquisitions by 74% over five years in a 10-facility network model (83). Furthermore, similar mathematical models projected that adopting a coordinated containment according to the CDC guidance (84) that incorporated the interfacility communication and screening would result in a 76% reduction of transmission of targeted MDROs in three years (35). Knowing which facilities share the most patients and identifying types of patient sharing connections associated with CRE transmission are crucial to designing multi-facility containment efforts (82,83). Nevertheless, tracking the historical movement of patients requires computational resources and access to patient identifiers to link patient admissions in large databases, and the construction of a patient-sharing network requires programming software and expertise to construct and analyze network data (85).

Infectious disease epidemiologists have commonly used social or sexual networks among high-risk individuals to understand the spread of HIV or sexually transmitted infections. In recent years, more researchers have incorporated networks to understand the transmissions of infectious diseases. Since MDROs are amplified in healthcare settings, it is more practical to use the patient-sharing network structure to understand the transmission of MDROs. However, the existing patient sharing networks in literature have limitations; they have been constructed from admissions data in the general population covered by specific type of insurance (86,87), include only a small geographic area (86,88), include only direct transfers (2,86,87,89), or only involve the movement of patients across hospitals (2,56).

Table 3 includes publications that reported the association between a facility-level measure of connectedness, or centrality measures, within a patient-sharing network and CRE incidence. Most studies found a positive association between a facility's high volume of incoming transfers, quantified as the centrality measures as indegree or weighted indegree, with CRE or MDRO

incidence (2,89,90). In one study, CRE incidence correlated with betweenness, another centrality measure that quantifies how often a facility lies between the paths between two other facilities (86). These findings support the argument that patient-sharing network plays a role in MDRO transmissions, but these positive associations are expected and lack specificity. It is still unclear how the characteristics of ties between facilities, for example, reciprocated relationship versus one-sided transfer pattern, or connections between different types of facilities are associated with facility-level CRE prevalence.

These studies also adjusted their analysis on hospital-level covariates that may confound the relationship between network statistics and CRE incidence. In conclusion, it is essential to fit a better model to assess the association between the intrafacility risk of CRE and the measure of connectedness in a patient-sharing network.

Table 1.3 Summary of Studies on the Association Between Facility-Level Patient-sharing network and MDRO Incidence

Author, Year	Included Facilities	Transfer Data Source	Primary exposure (s)	Facility-Level Outcome	Covariates	Transfers	Effect Measures
Ray, 2016 (90)	ACHs and LTACHs in Chicago, Illinois	Illinois HDDS 2013	Degree	CRE cases per 10,000 patient-days	Number of beds, urban locations, county type, number of patients shared with LTACHs	Indirect: 90 days	RR: 1.056(95% CI 1.003-1.08) for rural facilities; 1.03(95% CI 1.002- 1.05) for urban facilities
Bower, 2020(86)	ACH, LTACH, LTCF in Atlanta, Georgia (n=99)	CMS Medicare Data	Betweenness	CRE incidence	Log of patient-days as the offset for a specific facility, stratified by facility type, connectivity metrics categorized into quartile	Direct Indirect: 365 days	Correlation coefficient r=0.75 p-value <0.01 for ACH, r=0.77, p-value =.03 for LTACHs
Simmering, 2015 (2)	Hospitals in California	Healthcare Costs and Utilization Project Inpatient Database, 2005-2011	Log Indegree, Log Weighted Indegree	Mean CDI cases by quarter	Log of the fraction of patient 65 years and older, log of hospital median length of stay, log-transformed number of hospital admission in the quarter	Direct	IRR: 1.048 (95%CI 1.023-1.074) for log indegree, I IRR: 1.033(95% CI 1.015-1.052) for log weighted indegree
Fernandez-Garcia, 2017 (87)	Acute medical or surgical facilities in the United States	CMS MedPAR 2006 and 2007	Mean incidence at connected hospitals in transfer network	CDI incidence	hospital size, different geographical distance between hospital pairs	Direct	OR: 1.34 (95% CI plotted, not reported) at a distance of 100 kilometers
Didiodato, 2018 (89)	Eleven academic and 41 community hospitals in Ontario, Canada	Ontario Ministry of Health and Long-Term care and EMS service	CDI score, modified from weighted indegree and number of previous year's CDI cases	CDI events for each calendar year	Availability of *C. difficile* stool assay in the facility, antimicrobial stewardship program.	Direct	IRR: 1.045 (95% CI 1.009-1.085) for academic hospitals; 1.036 (95% CI: 1.003-1.07) for community hospitals

Abbreviations: MDRO, multidrug-resistant organism; ACH, acute care hospitals; LTACH, long-term acute care hospitals; HDDS, hospital discharge data system; RR, risk ratio; IRR, incidence risk ratio; OR, odds ratio; CMS, Centers for Medicare and Medicaid Services; MedPAR, Medicare Provider Analysis and Review; CDI, *Clostridiodes difficile* infections; EMS, Emergency Medical Services; r, correlation coefficient; CI, confidence interval

CHAPTER 2

First Aim: The Re-admissions of Patients with Carbapenem-Resistant Enterobacterales

2.1 Overview

The study in this chapter included the first study aim, which was to assess the set of patient characteristics associated with hospital re-admissions among patients infected or colonized by Carbapenem-Resistant Enterobacterales (CRE). The patient characteristics associated with the first hospital re-admission among CRE patients were used to subset the general patient population into a CRE surrogate population.

The PSNs used to identify at-risk facilities of CRE transmissions are often constructed from general patient hospitalization data. Studies assessing the association of connectedness measures and the facility-level MDRO prevalence showed a modest association (1,2,86,89). PSNs constructed from the general patient population may be limited because patients with CRE acquisition have different characteristics and healthcare exposures than the general hospitalized patient population (84,91). Older adults and patients with underlying chronic illnesses are disproportionally affected by CRE (11,92). These patients may encounter more acute care hospitals and long-term care settings for rehabilitation or skilled nursing care (11,82,93). The reporting of CRE acquisition, mainly CRE colonization, can often be incomplete and not always available to public health departments. Therefore, PSN analysis using the hospitalization of patients with similar characteristics to patients with CRE acquisition can help identify at-risk facilities for containment efforts.

To analyze a PSN with similar transfer patterns to patients with CRE acquisition, we identified the characteristics associated with hospitalizations within 12 months since CRE was detected among patients with prevalent CRE infections. The patient characteristics associated with patient re-admission were analyzed using a multivariable survival regression model. The patient characteristics included in the final model were selected using a multistep assessment of a priori knowledge regarding risk factors of re-admissions among MDRO patients, descriptive analyses, and bivariate association with the outcome. The results of the first aim informed the following dissertation aims.

Publications characterizing the demographics, hospitalizations, and outcomes of CRE patients are commonly conducted in tertiary care hospitals and rarely analyze patient re-admissions after the initial infection, especially to other healthcare facilities. In this aim, the data set allows tracing of inpatient and outpatient hospitalizations of CRE patients before CRE was identified. Furthermore, because the data covers all hospitals in Tennessee, hospitalization and patient outcomes can be followed beyond the index facility. We reported the study methods and findings using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

2.2 Objectives

The primary study objective was to assess the patient characteristics associated with hospital re-admission within 12 months among CRE patients. Meanwhile, the secondary objectives are:

1) To identify the demographic and clinical characteristics of CRE patients in Tennessee and hospitalizations occurring within 12 months after the index date
2) To compare patients' demographic and hospitalization characteristics who had carbapenemase-producing CRE (CP-CRE) versus non-CP-CRE isolates.
3) To quantify the frequency of patients with stays at long-term care facilities before and after CRE identification among CRE patients
4) To quantify and characterize the cumulative number of inpatient days within 12 months after CRE was identified

The research question of this study aim was formulated as a Population, Intervention, Comparator, Timing, and Setting (PICOTS) statement listed in

Table 2.1

Table 2.1 First Aim Research Question as PICOTs statement

Population	Patients reported to the Tennessee Department of Health surveillance system as having CRE infection or colonization based on the type of specimen. Cases with only rectal isolates are considered colonized patients, while all other clinical isolates are considered infections.
Intervention/ Exposure	Covariates were evaluated simultaneously without having one primary exposure. A priori knowledge from the literature of the clinical and demographic characteristics that were risk factors to re-admission and re-infection among CRE-infected individuals were included as the initial set of potential predictors. These included but are not limited to patient age, race and ethnicity, sex, underlying conditions, previous healthcare exposures, sepsis diagnosis during initial hospitalization, length of hospitalization, and nursing home stays.
Comparator	Patients were evaluated subgroups to see whether the re-admission rates significantly varied across groups and needed to be modeled separately. The potential stratification may be based on several characteristics, including: - inpatient hospitalization status at baseline - carbapenemase production status - infection or colonization isolates.
Outcome	Time to the first inpatient hospitalization within 12 months of the index date. The follow-up starts on the index date, defined as the hospital discharge date for hospitalized patients, or isolate collection date for non-hospitalized patients. Secondary outcomes evaluated include the time between each hospitalization discharge date and re-admissions and the proportion of cases re-admitted within 90, 180, or 365 days.
Timing	Cases with the first isolate collected during July 2015 – September 2019 were included. Exposure covariates were gathered from the TN hospital discharge data from July 2014 – December 2019, allowing 12 months of

	exposure data collected from the earliest cases. Patient death information is gathered from TN vital records from July 2015 to December 2019, allowing for follow-up for at least three months for all subjects.
Setting	The state of Tennessee.

2.3 Retrospective cohort construction using multi-database linkage

2.3.1 Case Definition

The data source for patient identifiers and microbiologic information of patients with CRE infection or colonization is the Tennessee Department of Health (TDH) statewide infectious and reportable diseases surveillance system, which operates using the National Disease Surveillance System–Base System (NBS) database. We included patients with their first CRE positive culture collected between July 2015–September 2019. CRE is a reportable condition in Tennessee, and isolate submission is required for confirmatory and molecular testing at the State Public Health Laboratory. CRE acquisition was defined using the 2015 Council of State and Territorial Epidemiologists (CSTE) case definition (59). Patients with CRE colonization and infection were both included in the study as CRE acquisition and not differentiated in the analysis.

Tennessee uses the National Disease Surveillance System (NEDDS)–Base System (NBS) developed by the CDC to manage reportable conditions. CRE has been a reportable disease in Tennessee since 2011, which means that all healthcare providers and laboratories should immediately report CRE-positive isolates from patients treated in Tennessee to the local or state health department.

> "*Enterobacter spp, E.coli or Klebsiella spp*: Resistant to any carbapenem (minimum inhibitory concentrations of ≥4 mcg/ml for meropenem, imipenem, and doripenem or ≥ 2 mcg/ml for ertapenem), or
>
> *Production of a carbapenemase (e.g., KPC, NDM, VIM, IMP, OXA-48) demonstrated by a recognized test (e.g., polymerase chain reaction, Metallo-β-lactamase test, modified Hodge test, Carba NP)"* (94).

Additionally, the characterization of CP-CRE is based on the CDC/CSTE 2017 position statement:

"Carbapenemase Producing Carbapenem-Resistant Enterobacterales (CP-CRE) is defined as E. coli, Klebsiella spp., or Enterobacter spp. where the isolate is:

- *positive for carbapenemase production by a phenotypic method, or*
- *positive for a known carbapenemase resistance mechanism by a recognized test*" (95)

Isolates collected within since the first isolate collection was notified to TDH were grouped into one occurrence (or one case) in NBS. Patients were grouped as colonized or infected based on the isolates collected during their first CRE occurrence. Colonized patients only reported rectal isolates, while infected patients reported at least one clinical isolate. Isolates collected from the respiratory tract, blood, urinary tract, soft tissues, or normally sterile sites were considered clinical isolates. Because the surveillance data did not provide longitudinal data before the patients first acquired CRE, we could not ascertain CRE incidence, and CRE cases were deemed as prevalent events.

In practice, CRE was primarily reported to TDH either electronically or through faxed laboratory reports by clinical laboratories. These laboratories performed susceptibility tests of bacterial isolates from a patient's body site for diagnostic or screening purposes. Most have a data stream to the TDH surveillance system to automatically send an electronic laboratory report when they tested a bacterial isolate resistant to carbapenem antibiotics. In addition to sending lab reports, laboratories should submit CRE isolates to the State Public Health Laboratory (SPHL) for carbapenemase testing. When carbapenemase production was detected, or the gene conferred carbapenemase production was identified, TDH epidemiologists assigned the case as a CP-CRE. They contacted the facility to request infection preventionists to gather healthcare exposures or healthcare contacts information. At the time of this dissertation, clinical laboratories do not universally perform carbapenemase.

Patients whose first positive CRE isolate was collected in July 2015, when the SPHL started performing the modified Carbapenem Inhibition Method (mCIM) test to identify carbapenemase production, were included. Of the available assays, mCIM has the highest sensitivity and specificity to detect carbapenemase production compared to the gold standard of DNA sequencing (97). Patients with bacterial isolate collection dates after September 30 2019

were hospital discharge data (HDDS) is only available until December 2019 at the time of the study to allow at least three months of Database linkage

Information on healthcare exposures, underlying conditions, hospitalization details, and patient outcomes was gathered by linking patient identifiers from NBS to the statewide Hospital Discharge Data System (HDDS) and vital records (VR). HDDS records included all inpatient and outpatient admissions to all hospitals licensed by the State of Tennessee, including short-term acute care hospitals (STACHs), inpatient rehabilitation facilities, and long-term acute care hospitals (LTACHs). HDDS did not include patient admissions at skilled nursing facilities (SNFs) but captured hospitalization discharges to SNFs.

Personal identifiers of CRE patients were linked with hospitalization data from the HDDS and VR using the combination of date of birth, sex, and full name. Data linkage yielded at least one hospitalization for 2,804 CRE patients with complete identifiers for 2,520 (90%) patients. The remainder of unlinked patients were unlikely to have any inpatient or outpatient hospitalizations in Tennessee during the timeframe of interest. The 10% without matching hospitalization were either (1) cases were identified in the nursing homes treated in hospitals in neighboring states. Patients who did not have any hospitalization during the study period are considered outpatients who did not develop the primary outcome. Their available characteristics were included in the descriptive analysis. Figure 2.1 illustrates the database linkage timeline to construct the retrospective cohort.

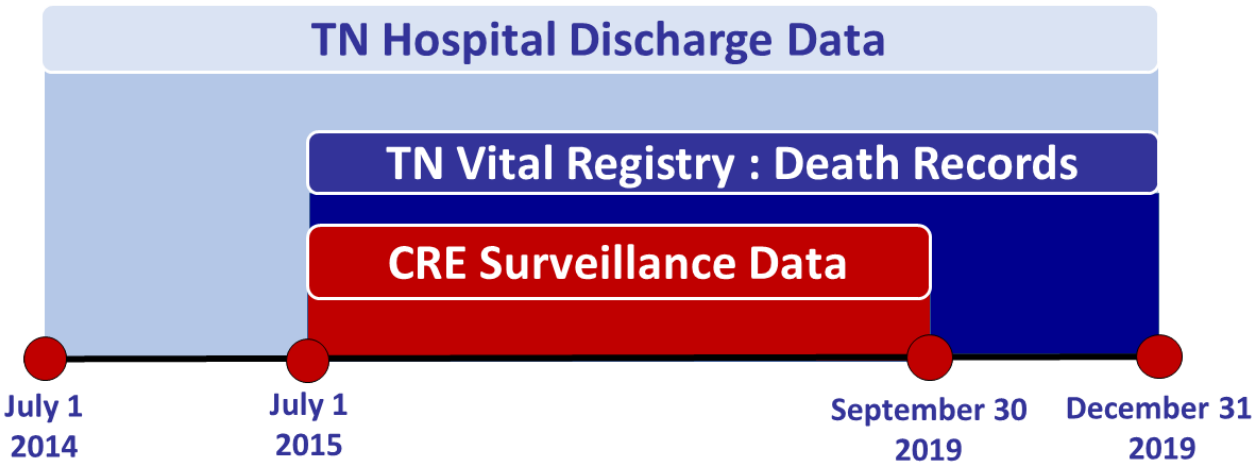


Figure 2.1 Database Linkage Timeline to Construct Retrospective Cohort

2.3.2 Data Management

Raw datasets containing Protected Health Information (PHI) were transformed, cleaned, and linked within the TDH server. Patient-level datasets were accessible only to the TDH staff and students whom the Institutional Review Board approved as part of the research project. The datasets can be accessed when connected to the TDH server. The primary investigator for the TDH projects related to this dissertation is Dr. Pamela Talley, the TDH Healthcare-Associated Infections and Antimicrobial Resistance (HAI-AR) program interim director. Dr. Talley has access to all raw and final datasets for analysis. Other HAI-AR epidemiologists listed in this project's IRB also have access to all datasets. Aggregate datasets without patient-level data can be shared with CDC partners involved in the projects based on the existing EIP data use agreement between TDH and CDC. All committee members can also review the reports from the data analysis and the codes used to generate them.

Raw and final datasets with patient-level data with and without PHI were stored in a shared network drive accessible to TDH HAI staff. The study has received IRB approval from TDH IRB (IRB# 2020-0242 and 2019-0168).

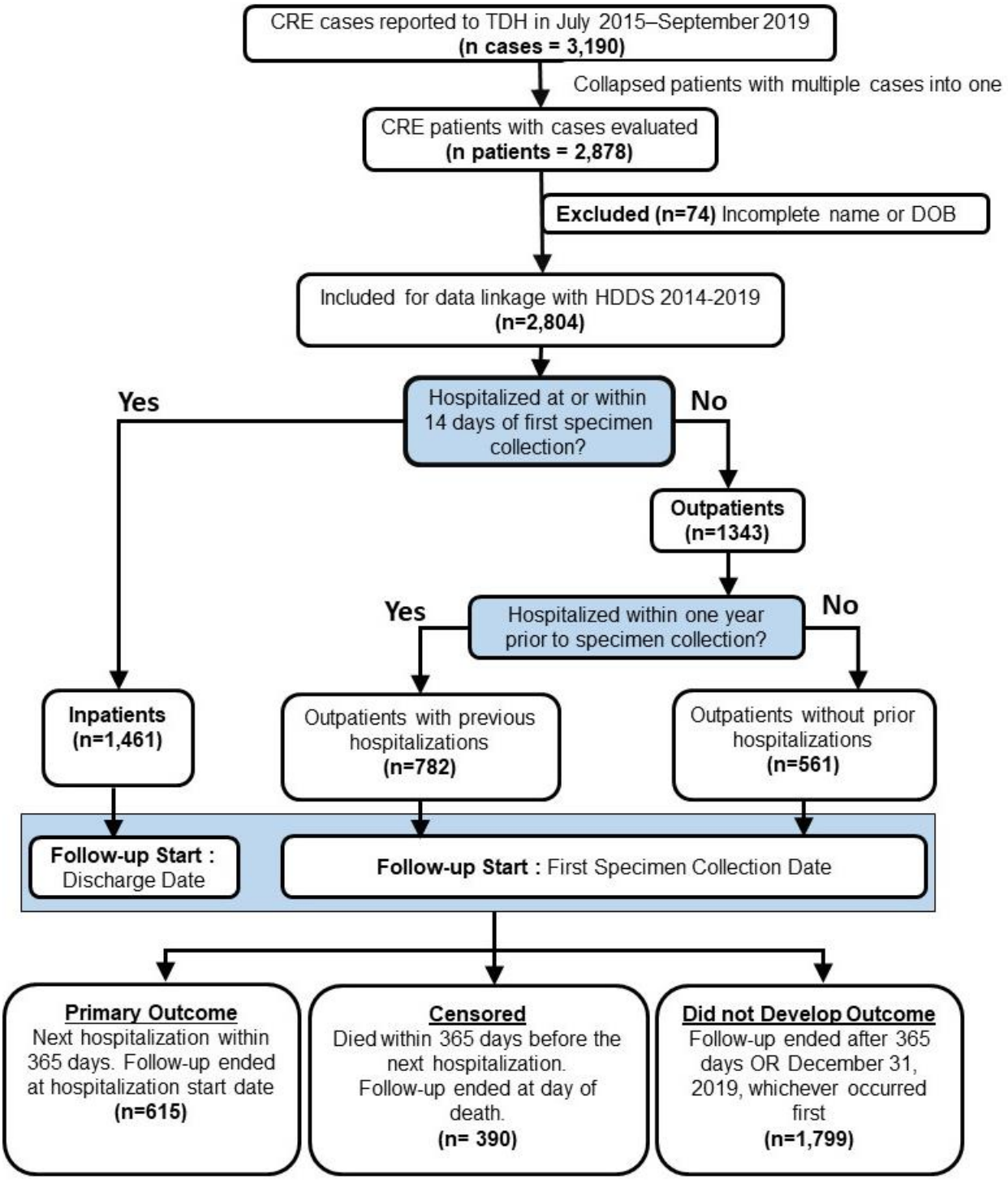


Figure 2.2 Study Diagram

2.4 Patient outcomes

The primary study outcome was the first subsequent hospitalization for any cause within 12 months after the index date. The index date was the discharge date of the hospitalization during which the first CRE positive culture was collected, or if the patients were not hospitalized during specimen collection, the discharge date of hospitalization which began within 14 days after first CRE culture collection date. The 14-day window was derived from the CDC National Healthcare Safety Network definition for the window of isolates associated with the same infection or healthcare exposures. Alternatively, if they were not hospitalized, the index date is the first isolate collection date (98). Figure 2.3 provides the schematics of the determination of index date.

Patients were followed until the index date of the first hospital re-admission date within 365 days, 12 months since their index date, or the date of death, whichever occurred first. The maximum follow-up length of 365 days is derived from the study findings on the duration of CRE colonization and patient re-admission rates (see Chapter 1) (29). Patients who died before the discharge date of the index hospitalization were censored at baseline and contributed 0 days of follow-up, thus excluded from the analysis. Patients who died before their subsequent hospitalization were considered were censored on their day of death.

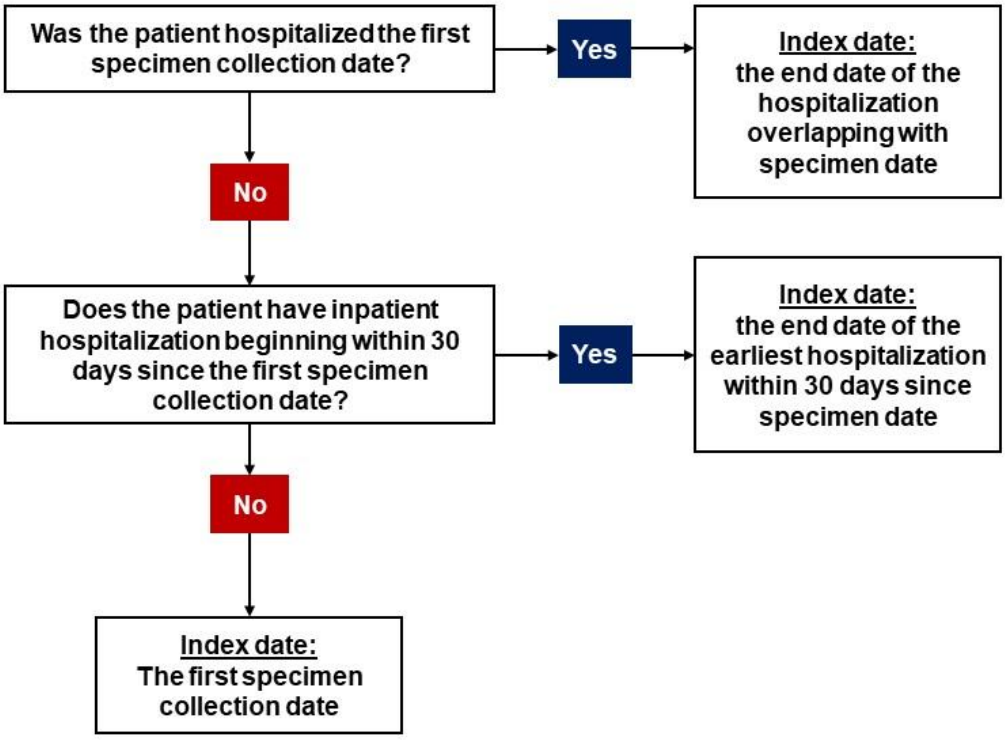


Figure 2.3 Index Date Determination

2.5 Data Analysis Overview

A priori knowledge on predictors of re-admissions among patients with CRE acquisitions or prevalent infections and data-driven considerations determined the final form and predictors of the multivariable model to fulfill the objective of Aim 1. The steps to evaluate and select the variables for the final model are detailed in the following chapter sections. Patient characteristics were assessed in each stage to choose a subset that meets the criteria evaluated. Next, a subset of selected patient characteristics was assessed in the next step, and so on. These data analysis steps were:

- Step 1: Collect and clean the data on the potential predictors
- Step 2: Select CRE patient characteristics that are found in the general patient population
- Step 3: Evaluate correlations among predictors and perform data reduction of highly correlated predictors
- Step 4: Test for the bivariate association of each predictor with the primary outcome

- Step 5: Build a parsimonious multivariable model to choose the final sets of predictors

Data linkages and cleaning were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina). Statistical analyses, including multiple imputations, were performed using R statistical software, version 4.2.5 (Vienna, Austria; http://www.R-project.org).

2.6 Step 1: Collect and clean the data on the potential predictors

2.6.1 Select the initial set of potential predictors

CRE patient characteristics were analyzed to subset CRE surrogates from the general patient population. Therefore, only the patient characteristics collected in the HDDS dataset from the general patient population were evaluated among CRE patients as potential predictors. The information gathered from the laboratory regarding specific carbapenemase testing results and antimicrobial susceptibility of the isolate was described but not evaluated as potential predictors.

We reviewed all patient information listed in the raw surveillance and administrative datasets as potential predictors. However, the initial set of potential predictors was included based on the findings from existing literature on factors associated with CRE infections and re-admissions of CRE patients. We evaluated an initial set of 41 predictors likely to influence the risk of CRE acquisition and readmissions among CRE-infected patients based on *a priori* knowledge in the literature. These include patient demographics, primary insurance, underlying conditions, sepsis during the index hospitalization caused by any pathogen, and previous healthcare exposures (11,43,92). We extracted 17 conditions that composed the Deyo-Charlson Comorbidity Index (DCCI) from the International Classification of Diseases (ICD)-9 and ICD-10 diagnostic codes in HDDS discharge diagnoses before the first specimen collection date (99,100). Each condition was coded as dichotomous variables and as a composite DCCI score.

Previous SNF stays were identified from three sources: identification of SNF as the ordering facility in the culture laboratory reports submitted to the TDH surveillance data, patient address matching a registered SNF address, or discharge to SNF in HDDS within 12 months preceding their first specimen collection. Healthcare exposures within 12 months before the first

specimen collection date, including emergency department visits, inpatient hospitalizations, the total length of stay (LOS) at STACHs, and total LOS at LTACHs, were extracted from HDDS. Specific healthcare procedures were extracted from ICD-10-Procedure Coding System (PCS) and ICD-9 or ICD-10 discharge diagnoses (Supplementary Material, Appendix 1). The SAS programming code to gather comorbidity information from the International Classification of Diseases (ICD)-9 and -10 codes listed as discharge diagnoses was validated in a published study and made available to the public by the authors (99).

2.6.2 Variable transformation and cleaning

Variables selected for the initial predictors were transformed based on the data distribution and the practical application to subset the general patient population. We evaluated whether data transformation was required for the essential continuous variables into logarithmic scales and splines to fit the data better. The use of cubic splines was evaluated for a robust continuous predictor, e.g., patient age, by comparing the AIC value with the model with linear terms. We found no need to conduct such a transformation. The primary payer of patient hospitalizations was listed in the raw data as separate coding for each company or government insurance. We categorized primary insurance coverage into broader categories: commercial, Medicare or Medicaid, self-pay or uninsured. The initial predictors evaluated for the study in this step, detailed in this step, including the variable transformation, is listed in Table 2.2.

Table 2.2 List of Initial Predictors and Data Transformation

Variables	Source	Variable Type and Coding after cleaning
Demographics		
Age	NBS and HDDS	Continuous
Sex	NBS and HDDS	Binary; Female = 1
Race	Provider-reported in HDDS	Categorical; White=1, Black=2, Asian and Pacific Islander=3, Others=4
Ethnicity	Provider-reported in HDDS	Binary; Hispanic=1; unknown and non-Hispanic=0
Insurance	HDDS	Categorical; Medicare or Medicaid =1, Commercial=2; Uninsured/Self-Pay=3, Others=4
Healthcare Exposures within 12 Months before First Specimen Collection Date		
Hospital type	HDDS	Categorical; 1= Acute care hospital; 2= Long-Term Acute Care hospitals; 3= Inpatient rehabilitation, Critical access hospital, and psychiatric hospital
Length of index hospitalization	HDDS	Integer, in days
Sepsis	HDDS; ICD 9 and ICD-19 code starting with the following – Bacteremia: 7907, R788; Septicemia: 038; SIRS: 9959, R652, R651; Sepsis 9959, A41,	Binary, 1=Yes

	A5486 , A021, T814,O753, O03, O04, O05, O06, O07, O08, T880, T802, O85, A40,A427, A227, B377, A267, A282,B007, A327,A241, A392, A393, A394, A207, A217, A483; Sepsis in Newborn: P36;Septic Shock:9959, 78552, R6521, R6520;Post-Procedure Sepsis T8144	
Hospital location	HDDS hospital registration matched with county rural or urban status in census data	Binary; 1=Urban or mostly urban, 0= Rural or mostly rural
Any prior hospitalization	HDDS Dataset	Binary; Yes=1
Number of prior STACH hospitalizations	HDDS Dataset	Integer (count)
Duration of prior STACH hospitalizations	HDDS Dataset	Integer, in days
Number of prior LTACH hospitalizations	HDDS Dataset	Integer (count)
Duration of prior LTACH hospitalizations	HDDS Dataset	Integer, in days
Gastrointestinal Endoscopy	HDDS ICD-10 PCS Codes: First two digits of Procedure Codes: OD and 5th digits: 4,6, or 8.	Binary; Yes=1
Indwelling Catheters	ICD-9 or 10 PCS Codes starting with T83011, T83021, T83031, T83091, T83112, T83022, T83192, T83511, T83592, 3C, 8C, Z466	Binary; Yes=1
Urinary catheter	HDDS ICD-10 PCS Codes Starting with (0T9, 0T2, 0TP, 0TH, 5794; or ICD-9 or ICD-10 Diagnostic Codes T830, T835	Binary; Yes=1
Central Venous Access	ICD-10 PCS codes starting with: 4A04, 4A14, 02HV, 06H0, ICD-9 or 10 Diagnostic Codes starting with: T8021	Binary; Yes=1

Dialysis	ICD-10-PCS codes starting with: Z992, R880, T824, 5A1D, 3995	Binary; Yes=1
LTACH hospitalization	HDDS Hospital Types in HDDS and TDH licensure database	Binary; Yes=1
Nursing Home Residence	HDDS Discharge Status and/or matched geocoded patient residence in NBS surveillance data with nursing home address	Binary; Yes=1
Underlying Conditions		
Any underlying conditions	HDDS Diagnostic ICD Codes; Summarized and calculated into a score using a validated SAS code	Binary; Yes=1
Acute myocardial infarction	First digits of ICD diagnostic codes: 'I21', 'I22','I252','410','412'	Binary; Yes=1
Congestive heart failure	First digits of ICD diagnostic codes: I43, I50, I099, I110, I132, I132, I255, I420, I425, I426, I427, I428, I432, P320, 39891, 40201, 40211, 40321, 40401, 40403, 40411, 40413, 40491, 40493, 4254, 4255, 4257, 4258, 4259, 428	Binary; Yes=1
Peripheral vascular disease	First digits of ICD diagnostic codes: I70, I71, I732, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959, 0932, 4373, 440, 441, 4432, 4432, 4438, 4439, 4471, 5571, 5579, V434	Binary; Yes=1
Cerebrovascular disease	First digits of ICD diagnostic codes: G45, G46, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69, H340, 0932, 4373, 440, 441, 4432, 4432, 4438, 4439, 4471, 5571, 5579, V434	Binary; Yes=1
Dementia	First digits of ICD diagnostic codes: F00, F01, F02, F03, G32, F051, G321, 320, 3241, 3422	Binary; Yes=1
Chronic lung disease	First digits of ICD diagnostic codes: J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67I278, I279, J684, J701, J703,	Binary; Yes=1

	4168, 4169, 490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505, 5064, 5081, 5088	
Rheumatic disease	First digits of ICD diagnostic codes: M05, M32, M34, M34, M06, M325, M351, M353, M360, 4465, 7100, 7101, 7102, 7103, 7104, 7140, 7141, 7142, 7148, 725	Binary; Yes=1
Peptic ulcer	K25, K26, K27, K28, 532, 532, 534, 534	Binary; Yes=1
Mild liver disease	First digits of ICD diagnostic codes: B18, K73, K74, K700, K701, K702, K703, K709, K717, K713, K714, K715, K760, K762, K763, K764, K768, K769, Z944, 07022, 07023, 07032, 07034, 07044, 07054, 0706, 0709, 570, 571, 5734, 5734, 5738, 5739, V427	Binary; Yes=1
Diabetes without complications	First digits of ICD diagnostic codes: E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E132, E132, E132, E136, E138, E139, E140, E141, E146, E148, E149, 2500, 2501, 2502, 2503, 2508, 2509	Binary; Yes=1
Diabetes with chronic complications	First digits of ICD diagnostic codes: E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E122, E123, E124, E125, E127, E132, E134, E134, E135, E137, E142, E143, E144, E145, E147, 2504, 2505, 2506, 2507	Binary; Yes=1
Paralysis	First digits of ICD diagnostic codes: G81, G82, G041, G114, G801, G802, G832, G832, G832, G834, G834, G839	Binary; Yes=1
Renal disease	First digits of ICD diagnostic codes: N18, N19, N052, N053, N054, N055, N056, N057, N250, I120, I132, N032, N034, N034, N035, N036,	Binary; Yes=1

	N037, Z490, Z491, Z492, Z940, Z992, 3441, 342, 343, 3440, 3441, 3442, 3443, 3444, 3445, 3446, 3449, 40321, 40321, 40391, 40402, 40403, 40412, 40413, 40492, 40493, 582, 5832, 5832, 5832, 5834, 5836, 5837, 585, 586, 5880, V420, V451, V56	
Malignant tumors	First digits of ICD diagnostic codes: C00, C01, C02–C26, C32, C34, C37–C58, C60–C76, C81, C82, C83, C84, C85, C88, C90–C97, 140–165, 170– 195, 200–208, 2386	Binary; Yes=1
Moderate to severe liver disease	First digits of ICD diagnostic codes: K704, K711, K721, K732, K765, K766, K767, I850, I859, I864, I982, 4560, 4561, 4562, 5722, 5723, 5724, 5728	Binary; Yes=1
Solid metastatic tumor	First digits of ICD diagnostic codes: C77, C78, C79, C80, 196, 197, 198, 199	Binary; Yes=1
AIDS	First digits of ICD diagnostic codes: B20, B21, B22, B24, 042, 043, 044	Binary; Yes=1
Charlson-Deyo Comorbidity Index	Scoring calculation in literature (99)	Integer; Range = 0-15.

2.7 Step 2: Select characteristics found in the general patient population

We only included CRE patient characteristics in the model if they can be used to subset the general inpatient population in HDDS into a CRE surrogate population. Therefore, underlying conditions and procedures reported in less than 4% of the adult general inpatient population in 2016–2019 HDDS were excluded. Children were not analyzed because CRE primarily affects adults. This prioritization was performed because the inclusion of less commonly found characteristics in the general population in our final model may result in difficulty to subset the CRE surrogate patients from the general population.

2.8 Step 3: Evaluate correlations among predictors

Some patient characteristics may be highly correlated and predictive of other variables. Some patients may have both congestive heart failure and renal diseases because they share common risk factors. Additionally, several comorbidities may result in hospitalizations requiring surgery or invasive medical device placement. Thus, we had expected some correlations between the predictors. Including both predictors may result in the multicollinearity of the model and inflate the standard errors of the regression estimates.

We conducted the Pearson correlation to all possible pairs of potential covariates to evaluate the correlations. We evaluated highly correlated predictor pairs (Pearson coefficient >=0.70) for possible multicollinearity. Deyo-Charlson Comorbidity Index (DCCI) was highly correlated with the number of underlying conditions (ρ=.95). Thus, we only included DCCI in the model because it was more frequently reported to be associated with adverse patient outcomes in literature (101–103). We also had two highly correlated variables that summarized healthcare exposures in LTACH within 12 months to first specimen collection, an integer variable of the length of stay and a binary variable of whether the patient was hospitalized. We included the integer variable as they provided more information on the magnitude of exposure.

2.9 Step 4: Test for the bivariate associations

We evaluated the bivariate associations between each predictor and the outcome variable. First, each predictor was evaluated using the Kaplan-Meier survival curve to describe the association between each predictor and the outcome and consider whether the assumption of proportional hazards over time may be violated in a Cox regression. Parallel or mostly parallel lines signaled proportional hazards of patient survival between the groups compared in the Kaplan-Meier survival curve. Univariable Cox regressions that only included each predictor of interest were used to evaluate the relationship between the potential predictors and the primary outcome. All variables with a Wald p-value less than 0.20 in Cox regression or log-rank p-value of less than 0.20 were evaluated in the next step.

2.10 Step 5: Build a multivariable model

2.10.1 Sample Size Justification and Power

Based on the findings from published literature, ~60% of CRE patients were re-admitted to the hospital within 12 months. With a projected sample size of 1700, we expected that approximately 1,020 patients would be re-hospitalized within 12 months after their index date. A more parsimonious model, defined as the fewest predictors with the maximal model fit, is desired as the final model. We aimed to fit at most one variable per 50 events, resulting in a maximum of 20 variables in the final model. The power calculation conducted using the Stata power command resulted in an estimated sample size of 1700 being required with an α of 0.05 to detect hazard ratios of 1.05 (represented as β=0.406) to 2 (β =0.69) and a range of event probabilities of 10%, 30%, and 60%, with a power of 80% or more; there would still be sufficient power to detect a moderate effect at the event probability of 0.3 or higher.

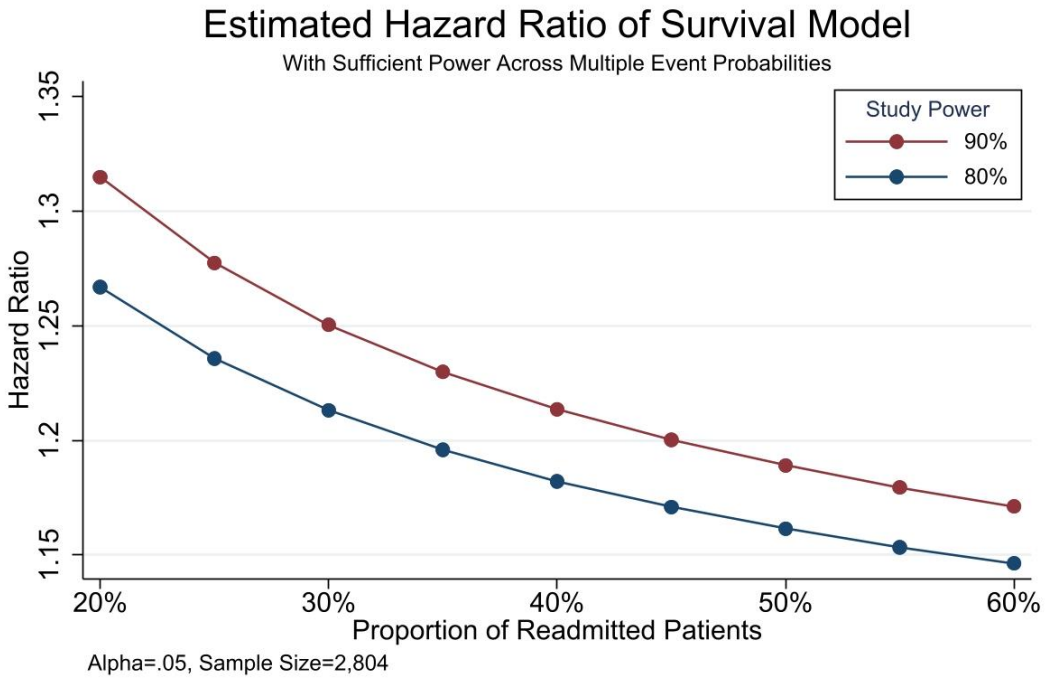


Figure 2.4 Estimated Effect Sizes for the Cox Proportional Hazard Regression

2.10.2 Model building

The final, parsimonious set of predictors was selected from the candidate set based on *a priori* knowledge of their association with CRE risks and the 4-step selection process from above. Bootstrap cross-validation was used to identify the model with the lowest Akaike Information Criterion (AIC). The bootstrap method included resampling the dataset with replacement and repeating the backward selection process 1500 times to identify predictors retained in the reduced model in each bootstrap sample. The final reduced model included the predictors consistently retained by the selection method and whose combination produced the lowest AIC.

2.10.3 Handling of Missing Data

We employed multiple imputations of missing data using the R MICE package. The proportion of missingness where the benefit of MI compared to the standard imputation technique is non-negligible is 5% or higher. However, simulation studies have suggested that thresholds should not be used to inform the decision to conduct multiple imputations. Observations with missing data at random were imputed using 30 iterations of the multiple imputation model. The linear prediction score (risk score) for each subject was calculated using the product of beta estimates (log-transformed hazard ratio) multiplied by the predictor values of each patient.

2.10.4 Model diagnostics

We evaluated the model for the fit with the proportional hazard (PH) assumption using its Schoenfeld residuals. The Cox model works under the assumption that the relationship between variables and the outcome is constant across time. Therefore, we also plotted the Schoenfeld residuals against time to rule out a time-dependent relationship for the residuals, violating the Cox proportional hazard assumption. An increasing or decreasing trend would suggest that the hazard ratio changes over time, and the proportional hazard assumption was violated. A p-value of <0.05 of Schoenfeld residual goodness-of-fit tests for the overall model and each predictor was deemed evidence of PH assumption violation. Additionally, we hypothesized that the baseline hazard differs between inpatient and outpatients. We evaluated whether the Cox model required stratification by index hospitalization status plotting the log of the negative log of the Kaplan-

Meier survival estimates against the log of time to observe the departure from PH assumption violation.

Receiver operating characteristic (ROC) curves were generated for the prediction of the outcome at 30, 90, 180, and 365 days since the index date, and the optimal risk score was selected to maximize Youden's index (sensitivity + specificity -1) at the 365 days (104). A model with an area under the curve (AUC) value of 0.5 has no discriminatory ability to predict the outcome. The values 0.7≤AUC< Hosmer and Lemeshow classified 0.8 as acceptable discriminative ability, and the increase in AUC value towards one means a better predictive ability (105).

Secondly, the model fit compared to observed data was checked by plotting the Kaplan-Meier (K-M) survival plots with the fitted survival. These two plots would ideally mostly overlap. The overlap between the two plots reflects how well the survival model fits with the observed data. Additionally, we plotted Cox-Snell residuals against the expected Nelson-Aalen cumulative hazard function estimates to examine the model's fit against the cumulative hazard function.

We plotted the deviance residuals against the linear predictor to find observed residuals outside the range (-2.5, +2.5), which signals observations highly influential to the model estimates. Additionally, influential observations were assessed by looking for the change in β $(\delta\beta)$ values of observations, especially the outliers.

The $\delta\beta$ value is the change in model estimate for the variable of interest if a specific observation is removed. Observations with extreme $\delta\beta$ values underwent sensitivity analysis by excluding them from the model and comparing the model fit and estimates with this observation and without.

2.11 Study Results

During the study period, 3,195 CRE cases representing 2,877 individual patients were reported to TDH. Seventy-four patients were excluded due to missing date of birth or name. We included 2,803 patients in the retrospective cohort, including 714 (25.5%) with CP-CRE acquisition. Nearly all (n=2,765, 98.4%) included patients had positive cultures from clinical specimens, and only 38 had rectal specimen, which likely represent CRE screening.

The breakdown of patient characteristics is shown in Table 2.3. The median age was 67 years old (interquartile range[IQR] 54–77), and 1,730 (61.7%) were females. Fifty-four percent (n=1,506) of patients were hospitalized during or within 14 days of their first specimen collection date. The majority (67.2%) of patients were Medicare or Medicaid beneficiaries, and 65.6% were non-Hispanic whites. Prior inpatient hospitalization was reported in 1,550 (55.3%) patients and 30.6% (n=858) had previous SNF stays. All measured healthcare exposures and underlying conditions were more common among inpatients than outpatients ($p<0.001$). Inpatients had shorter follow up (median 56, IQR 11–215) than outpatients (median 365, IQR 173–365). Twenty-six percent of outpatients were hospitalized, and 54.8% of inpatients were readmitted within one year. Among 825 inpatients who were readmitted, 60% were hospitalized in a different hospital than their index hospital.

Table 2.3 Characteristics of Patients with CRE Acquisition, Tennessee July 2015 – September 2019

Patient Characteristics	Inpatients	Outpatients	p-value*	Overall
n	1506	1297		2803
Female Sex (%)	849 (56.4)	881 (67.9)	<0.001	1730 (61.7)
Age (median [IQR])	66 [55, 76]	68 [52, 78]	0.238	67 [54, 77]
Race and Ethnicity (%)			<0.001	
Non-Hispanic White	1027 (68.2)	813 (62.7)		1840 (65.6)
Non-Hispanic Black	403 (26.8)	157 (12.1)		560 (20.0)
Hispanic/Other	73 (4.8)	34 (2.6)		107 (3.8)
Missing	3 (0.2)	293 (22.6)		296 (10.6)
Primary Insurance (%)			<0.001	
Medicare/Medicaid	1187 (78.8)	697 (53.7)		1884 (67.2)
Commercial	249 (16.5)	224 (17.3)		473 (16.9)
Uninsured	70 (4.6)	54 (4.2)		124 (4.4)
Missing	0 (0.0)	322 (24.8)		322 (11.5)
Carbapenemase Producers (CP-CRE) (%)	528 (35.1)	186 (14.3)	<0.001	714 (25.5)
Sepsis during Index Hospitalization (%)	627 (41.6)	0 (0.0)	<0.001	627 (22.4)
Died Within 1 Year (%)	606 (40.2)	136 (10.5)	<0.001	742 (26.5)
Hospitalized within One Year (%)	825 (54.8)	344 (26.5)	<0.001	1169 (41.7)
Healthcare Utilization within the Previous One Year				
Inpatient Hospitalization(s) (%)	1083 (71.9)	467 (36.0)	<0.001	1550 (55.3)
Total LOS at STACH, days (median [IQR])[$]	25 [10, 52]	14 [5, 30]	<0.001	21 [8, 45]
Previous LTACH Stays (%)	104 (6.9)	29 (2.2)	<0.001	133 (4.7)
Total LOS at LTACH, days (median [IQR])[$]	64 [47, 101]	70 [45, 112]	0.605	65 [46, 105]
Emergency Department Visits (%)	903 (60.0)	470 (36.2)	<0.001	1373 (49.0)
SNF Stays (%)	630 (41.8)	228 (17.6)	<0.001	858 (30.6)
Characteristics Among Patients >=1 Admission During the Study Period				
n	1506	1012		2518
Healthcare Procedures within the Previous One Year				
Dialysis (%)	145 (9.6)	25 (2.5)	<0.001	170 (6.8)
Urinary catheters (%)	169 (11.2)	72 (7.1)	0.001	241 (9.6)

Patient Characteristics	Inpatients	Outpatients	p-value*	Overall
Central Venous Access (%)	287 (19.1)	73 (7.2)	<0.001	360 (14.3)
Any Mechanical Ventilation (%)	209 (13.9)	52 (5.1)	<0.001	261 (10.4)
GI Endoscopy (%)	175 (11.6)	64 (6.3)	<0.001	239 (9.5)
Underlying Conditions				
Congestive Heart Failure (%)	621 (41.2)	234 (23.1)	<0.001	855 (34.0)
Dementia (%)	221 (14.7)	103 (10.2)	0.001	324 (12.9)
Chronic Pulmonary Disease (%)	657 (43.6)	282 (27.9)	<0.001	939 (37.3)
Paralysis (%)	242 (16.1)	78 (7.7)	<0.001	320 (12.7)
Renal Disease (%)	658 (43.7)	224 (22.1)	<0.001	882 (35.0)
HIV/AIDS (%)	10 (0.7)	2 (0.2)	0.170	12 (0.5)
Diabetes (%)	576 (38.2)	273 (27.0)	<0.001	849 (33.7)
Any Malignancy (%)	261 (17.3)	101 (10.0)	<0.001	362 (14.4)
Charlson Comorbidity Index (median [IQR])	4 [2, 7]	2 [0, 4]	<0.001	3 [1, 6]

Abbreviations: IQR, interquartile range; CP-CRE, Carbapenemase-Producing CRE; LOS, length of stay, STACHs, Short-Term Acute Care Hospitals; LTACHs, Long-Term Acute Cate Hospitals; SNF, skilled nursing facilities

*p-values were calculated using Kruskal-Wallis test for continuous variables and Chi-square for categorical variable.

$ The displayed median total Length of Stays at LTACHs and STACHs were calculated among patients with previous LTACH and STACH stays only, respectively.

The selection process identified seven predictors as risk factors for being hospitalized within 12 months: CCI, chronic lung disease, sepsis at index hospitalization, primary insurance (grouped into Medicare/Medicaid, commercial insurance, and uninsured), and four measures of healthcare exposures. These exposures include having at least one inpatient hospitalization, total LOS in LTACHs, total LOS in STACHs, and the use of urinary catheters (Table 2.4). The relationship between index hospitalization status violated the PH assumption. Therefore, the baseline hazard was stratified by index hospitalization status. All predictors in the final model had Schoenfeld residual p-values of >0.05, overall goodness-of-fit tests p-value of 0.09, and Harrell's C-index of 0.65.

Table 2.4 Unadjusted and Adjusted Hazard Ratios from Cox Regression Results

Patient Characteristics	Univariable Model			Multivariable Imputed Model		
	Unadjusted HR	(95% CI)	p-value	Adjusted HR	(95% CI)	p-value
Charlson Comorbidity Index	1.118	(1.1, 1.135)	<.0001	1.062	(1.042, 1.083)	<.0001
Chronic Lung Diseases	1.637	(1.457, 1.841)	<.0001	1.197	(1.056, 1.356)	<.01
Sepsis at Index Hospitalization	1.260	(1.095, 1.45)	<.01	1.219	(1.056, 1.406)	<.01
Primary Insurance, Ref: Medicare/Medicaid						
Commercial Insurance	0.616	(0.522, 0.728)	<.0001	0.773	(0.652, 0.918)	<.01
Uninsured	0.757	(0.572, 1.001)	0.0504	1.065	(0.795, 1.426)	0.6733
Prior Healthcare Exposures within 12 Months						
Inpatient Hospitalization	3.266	(2.837, 3.761)	<.0001	1.919	(1.646, 2.238)	<.0001
Total Length of STACH Stays	1.006	(1.005, 1.006)	<.0001	1.003	(1.002, 1.004)	<.0001
Total Length of LTACH Stays	1.002	(1, 1.005)	0.0653	0.998	(0.995, 1)	0.0768
Urinary Catheter	1.822	(1.543, 2.151)	<.0001	1.260	(1.062, 1.495)	<.01

Abbreviation: HR, hazard ratio; 95% CI (95% Confidence Interval); Ref, reference group; LOS, length of Stay; STACH, Short-Term Acute Care Hospitals; LTACH, Long-Term Acute Cate Hospitals

Note: The multivariable and univariable models were fitted using a stratified baseline hazard based on patient hospitalization status at baseline.

Ten percent (n=285) of included patients were outpatients without prior inpatient hospitalizations or ED visits during the study period; thus, we imputed their CCI, chronic lung disease, urinary catheter, and insurance status (Supplementary Material, Appendix 3). The risk factor with the largest hazard ratio (HR) in our model was previous inpatient stays (adjusted HR 1.92, 95% CI: 1.64–2.24). No hazard ratios changed beyond the third decimal digit except inpatient hospitalization, with adjusted HR of 1.87 (95% CI: 1.60, 2.18) in the complete-case model and 1.92 (95% CI: 1.64, 2.24) in the multiply imputed model.

Table 2.5 Final Model Results, Complete Case Analysis vs Multiple Imputed Model

Patient Characteristics	Complete Case Analysis		Multiple Imputed Model	
	Adjusted HR	(95% CI)	Adjusted HR	(95% CI)
Charlson Comorbidity Index	1.061	(1.041, 1.082)	1.062	(1.042, 1.083)
Chronic Lung Diseases	1.191	(1.051, 1.349)	1.197	(1.057, 1.357)
Sepsis at Index Hospitalization	1.251	(1.085, 1.441)	1.251	(1.086, 1.441)
Primary Insurance, Ref: Medicare/Medicaid				
Commercial Insurance	0.775	(0.653, 0.919)	0.773	(0.651, 0.917)
Uninsured	1.069	(0.799, 1.43)	1.063	(0.794, 1.423)
Healthcare Exposures in the Previous Year				
Inpatient stays	1.870	(1.604, 2.179)	1.918	(1.644, 2.236)
Total LOS at STACHs	1.003	(1.002, 1.004)	1.003	(1.002, 1.004)
Total LOS at LTACHs	0.997	(0.995, 1)	0.997	(0.995, 1)
Urinary Catheter	1.264	(1.065, 1.499)	1.262	(1.064, 1.498)

Abbreviations: CRE, Carbapenem-Resistant Enterobacterales; LTACHs, Long-Term Acute Care Facilities; CP-CRE, Carbapenem-Producing CRE; KPC, Klebsiella pneumonia Carbapenemase; STACHs, Short-Term Acute Care Hospitals; HR, hazard ratio; CI, confidence interval.

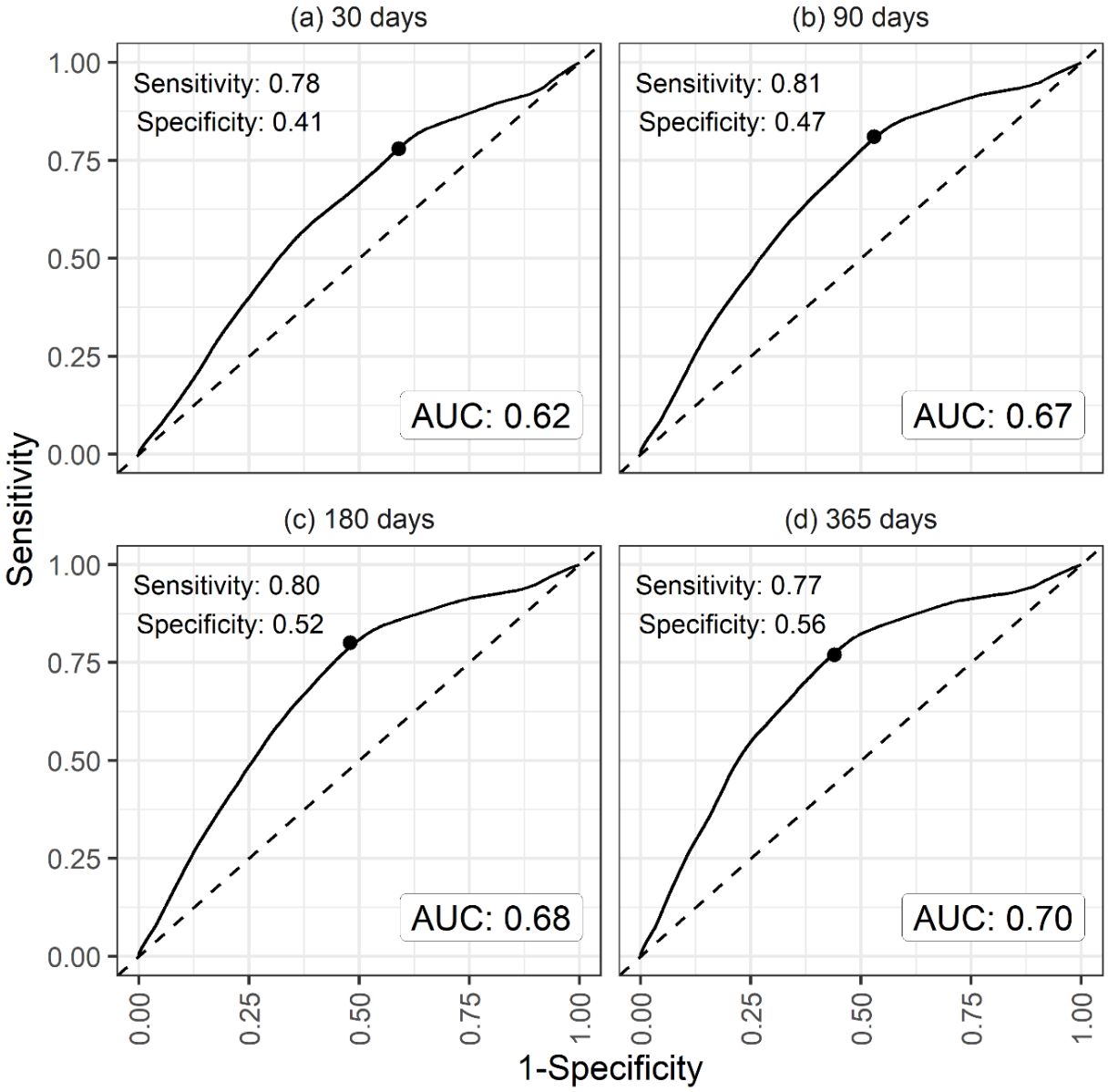


Figure 2.5 Receiving Operating Characteristic (ROC) Curve

Note: The ROC curve to classify Hospitalization within Different Follow-up Points (a) 30 days, (b) 90 days, (c) 180 days, and (d) 365 days. The numbers in the bottom right corner of each plot represent the area under the curve (AUC) of the survival model to discriminate the following hospitalizations of patients within the specified follow-up points. The solid line represents the sensitivity and specificity of different risk score cut-off values. The solid point represents the sensitivity and specificity of the optimal cut-off value of -0.22 to predict hospitalization within 365 days. The optimal cut-off value o the risk score was selected at each follow-up point to maximize the value of Youden's index (sensitivity + specificity -1) for the 365-day follow-up point.

2.12 Discussion

Identifying at-risk facilities from the patient sharing network (PSNs) patterns is essential for containment effort. PSNs currently available to identify these facilities can be improved by including a population that is representative of patients with CRE acquisition. The linkage of surveillance and administrative datasets could help identify the risk factors or re-admission or next hospitalization among patients with CRE acquisition. We can use these risk factors to construct PSNs from the hospitalization of patients with similar characteristics to those with CRE acquisition and improve the identification of at-risk facilities for CRE transmission and aide containment efforts.

The risk factors in our model are commonly collected in datasets available to public health entities such as hospital discharge data, the Centers for Medicare and Medicaid Services (CMS) claims data and the Healthcare Cost and Utilization Project (HCUP) dataset. Public health agencies or researchers can use the predictors we included in the final model to subset CRE surrogates and analyze their hospitalization patterns without having access to CRE case information. We also found that all-payer hospital discharge data may provide a more representative CRE surrogate population than single-payer datasets like CMS claims or commercial insurance database. Two-thirds of patients with CRE acquisition in this study had Medicare or Medicaid insurance, while the remaining were covered by either commercial insurance or uninsured. Therefore, the HCUP dataset or all-payer datasets are recommended source of PSN data to identify at-risk facility identification in the absence of access to statewide hospital discharge data.

A previous analysis by Wolford *et al.* found that the PSN from CRE cases is highly correlated with the CRE surrogate PSN (r=0.81) compared to the overall patient network (r=0.59) (106). Thus, we expect the PSN analyzed from the hospitalization patterns of CRE surrogates in our data would lead to better identification of at-risk facilities for CRE containment. Multivariable Cox model equation allowed calculation of individual patient risk scores among the general patient population and subset CRE surrogates based on their risk score. Figure 1 shows the sensitivity and specificity of the -0.22 risk score cutoff to predict hospitalizations at 30 days up to 365 days since index date among patients with CRE acquisition. The AUC value of the model at 365 days is acceptable (AUC=0.70) but underperformed at 30 days (AUC=0.62). The HCUP dataset, for

example, only reported re-admissions within 30 days. Therefore, this model should be used with some caution for predicting short-term re-hospitalizations. Nevertheless, without having access to CRE case information, CRE surrogates can be selected from the general population is by calculating the risk score of each hospitalized patient in the general population and include patients with risk scores higher than the cut-off value. To our knowledge, our study is the first to use a modeling approach and risk scores to subset the CRE population for PSN analysis.

Our study has several strengths. First, we were able to capture re-admissions to all TDH-licensed hospitals. Many studies on re-admissions of patients with CRE acquisition only captured re-admissions to the index facility. Furthermore, we successfully linked 90% of included patients to at least one inpatient or outpatient admissions. Ten percent of included patients were never hospitalized during the study period, which likely represented SNF residents or community-dwellers. This proportion is similar to the estimated 5.6–10.8% proportion of community-associated CRE cases in the United States in Kelley *et al.*'s systematic review (107).

The results of this study should be interpreted with the following limitations in mind. First, SNF stays were not included in HDDS, which means patients re-admissions to SNFs were not captured as patient outcomes. Long-term care facilities, including SNFs, were important reservoirs of regional CRE transmissions. Nevertheless, we used the information from the surveillance and hospitalization data to capture patient's previous SNF stays. The replication of this study with access to data on SNF stays may provide a more complete information of healthcare utilization among patients with CRE acquisition. Second, the ICD diagnostic and procedural codes were collected for billing purposes, not surveillance. Information on healthcare exposures was extracted from ICD-10-Procedural Coding System (PCS) codes in the billing records. Some procedures or diagnoses that are clinically important but do not result in significant reimbursement may be under-coded in HDDS. We tried to offset the procedures associated with lower reimbursement in ICD-10-PCS codes, such as urinary catheterization, by including related diagnostic codes from the ICD-10 diagnostic codes. In this instance, patients were coded to have a presence of urinary catheters if the procedures to insert urinary catheters were billed or if they were diagnosed with complications (catheter-associated infection) arising from urinary catheters (ICD-10 diagnostic codes). Validation studies of diagnostic codes in administrative datasets showed that underreporting is more common among patients with incomplete follow-up, like low-risk patients

or outpatients (108). Consequently, the effect sizes of our study may be overestimated away from the null. Despite their limitations, administrative datasets remain valuable and underutilized resources for investigating PSNs.

In conclusion, our study demonstrated the value of administrative and surveillance dataset to enhance the identification of at-risk facilities for CRE transmissions. Future research is needed to validate our methods in creating CRE surrogates and the utility of the PSN constructed from their hospitalization patterns in identifying at-risk facilities for CRE transmissions during actual outbreaks.

CHAPTER 3

Second Aim: The Association between Hospital Connectedness and CRE Prevalence

3.1 Overview

This chapter evaluates the association between hospital-level patient sharing network (PSN) metrics and hospital-level CRE prevalence. Patient sharing occurs when a patient is admitted to a hospital after being discharged from another hospital, either within one calendar day of being released (direct transfer) or after greater than one day in the community (indirect transfer). Every pair of hospitals have the potential to be connected through the patients they share, and these connections form a PSN.

Our specific aim for this study was to assess the causal association between hospital-level measures of connectedness with the prevalence of Carbapenem-Resistant Enterobacterales (CRE), one of the most urgent antimicrobial resistance organisms (AROs) threats in the United States. To conduct a social network analysis of patient sharing between hospitals in Tennessee, we aggregated hospitalization information from the hospital discharge data system (HDDS) into the number of transfers occurring between hospitals and transformed these data into network datasets. The main PSN of interest was constructed from the hospitalization pattern of patients with characteristics similar to patients with CRE infections or colonization. These patients represented the counterfactual population of CRE patients, referred to as CRE surrogates.

The primary hypothesis of this aim was centered on the specific network measure of hospital connectedness that combines the volume of incoming transfers and the number of hospitals that send transfers to a given hospital, represented as the metric called generalized indegree. The primary hypothesis was that the generalized indegree from the CRE surrogate network is associated with an increased risk of CRE events in each hospital.

3.2 Rationale and Objective

The association between magnitude or the diversity of interhospital patient transfers and ARO prevalence has been reported in cross-sectional studies in Chicago, Illinois (90), Orange County, California (2), and Ontario, Canada (89). These studies variably assessed the association between CRE prevalence with an increased number of hospital connections (90), number of incoming transfers(2), or other measures of connectedness (86,89). Some published PSN studies on AROs have defined transfers as patients hospitalized in another facility directly after discharge. In contrast, others included patients re-admitted after spending time in the community. Our study used 12 months as the maximum intervening stays to quantify transfers based on the length of documented CRE carriage (40,46,49).

Most PSN studies in the literature used a network constructed from the patient transfers of an entire patient population or a subset covered by specific insurance providers, i.e., fee-for-service Medicare and Medicaid (2,89,90). We sought to evaluate whether a PSN constructed from CRE surrogates reflected the movement of CRE patients across hospitals more accurately than the traditionally used population in literature. We assessed the association between CRE prevalence and the patient sharing network by analyzing multiple metrics of connectedness known as centrality measures. We hypothesized that centrality measures from the surrogate network have stronger associations with hospital-level CRE prevalence than networks constructed from the entire patient population or only Medicare and Medicaid beneficiaries.

Published studies on AROs and PSNs have modeled the association between the number of individual patient transfers or the number of hospitals that send transfers to a hospital. The known centrality measure associated with ARO prevalence is the number of transfers (weighted indegree). However, the measure of connectedness quantified for hospitals varied between published PSN studies. Therefore, we also addressed this variability by comparing the association of several centrality measures. We explored a novel measurement of a hospital's connectedness called generalized indegree to better capture the hospital's relative positioning within a network. Generalized indegree combines the number of individual patient transfers with the number of hospitals, by putting different weights of the importance the two measures though a modifiable tuning value, or α. As one of our secondary objectives, we evaluated a range of α values for generalized indegree for its association with CRE prevalence through statistical simulations. A

detailed explanation of generalized indegree is discussed in section 3.6.7. No other studies have compared the association of various centrality measures and PSNs or measured the association of the metric that incorporates both the volume of transfers and the number of hospitals that send incoming transfers in the form of generalized indegree.

In short, the study objectives are:

Primary Objective: To evaluate the independent association between the generalized indegree from a CRE surrogate PSN and next year's hospital-level CRE prevalence. Table 3.1 shows a detailed Population-Intervention, Comparison, Outcome, and Timeframe (PICOT) statement of the primary objective.

Secondary Objectives:

(1) To evaluate the optimal value of the α tuning parameter for generalized indegree with the strongest association with CRE prevalence after adjusting for confounders.
(2) To compare the association between the hospital CRE prevalence and the generalized indegree from the surrogate network against the association of CRE prevalence and generalized indegree from the general patient population network.
(3) To compare the association between CRE prevalence and generalized indegree with the CRE prevalence and other centrality measures within the same network.

The study objectives were achieved using an explanatory regression model using the data from the patient sharing network in 2018 and the CRE events reported in Tennessee during 2018. Although multiple years of data were available between 2015 and 2020, there have been changes in CRE data reporting and organizational factors that may have altered the patient sharing pattern. The State Public Health Laboratory (SPHL) began conducting carbapenemase production testing in July 2015. The test required clinical laboratories to submit CRE isolates.

Therefore, a multi-year analysis was unsuitable for a reliable assessment of our study objectives.

Table 3.1 PICOT statement of Aim 2

PICOT Element	Study Specifications
Population	Tennessee Hospitals with at least one hospitalization in the 2018 Hospital Discharge Data, including - Acute Care Hospitals (ACH), - Long-Term Acute Care Hospitals (LTACHs), - Inpatient Rehabilitation Unit (IRF), and Other hospital types
Intervention/ Exposure	**Primary Exposure:** Generalized indegree of the PSN constructed from CRE surrogate patient population movements (re-hospitalization) within 12 months **Secondary Exposures:** Weighted indegree, raw indegree, weighted outdegree, outdegree, betweenness, and eigenvector values from the same CRE surrogate PSN and the general population PSN in 2018
Covariates	The number of beds, patient-days, urban/rural location, teaching hospital status, CRE prevalence in the previous year, hospital types, and the proportion of incoming transfers from LTACHs
Outcome	The prevalence of CRE events attributed to each hospital in 2019 was calculated from the number of CRE events/ 1,000 patient-days in 2019
Timing	The outcome was assessed in 2019, and the exposures and covariates are from 2018
Setting	The state of Tennessee

Abbreviations: PICOT : Population, Intervention, Comparison, Outcome, and Time frame; PSN, patient sharing network; CRE, Carbapenem-Resistant Enterobacterales.

3.3 Study Population

The study population is hospitals licensed by Tennessee Department of Health, regardless of whether they reported CRE during the study period. Although each hospital is treated as one observation, some characteristics were aggregated from the patients treated at each hospital. We evaluated all hospitals with inpatient admissions during 2018 and 2019 in the Hospital Discharge Data System (HDDS). Because ownership changes, closures, and new openings of hospitals

resulted in the changes in reporting to HDDS, we additionally excluded hospitals that did not report hospitalizations for the entirety of 2018 and 2019. Furthermore, we excluded acute care hospitals with signs of incomplete reporting, those that transitioned to closed or another ownership status, and those having fewer than 365 hospitalizations in 2019 (less than one patient average per day). Of the 160 hospitals registered in the 2019 Tennessee licensure data, 144 hospitals were analyzed for PSN analysis.

3.3.1 CRE Surrogates

The CRE surrogate population was constructed using the results of the first study aim of to assess the risk factors of hospitalizations among patients with CRE acquisitions. In the multivariable Cox regression model in the first aim, the predictors associated with having subsequent hospitalization within 12 months among patients with CRE acquisitions were Deyo-Charlson Comorbidity Index (DCCI), chronic lung disease, sepsis at index hospitalization, the insurance that was listed as primary payer for patient's hospitalization, having at least one inpatient hospitalization in the last year, the total length of stay (LOS) in long-term acute care hospitals, total LOS in short-term acute care hospitals, and presence of a urinary catheter. The linear equations of the multivariable Cox model in the first aim were used to calculate the risk score for re-hospitalization within 12 months. We calculated the risk scores for each patient with CRE acquisitions from July 2015 to September 2019 and each patient with at least one inpatient hospitalization in the 2018 Hospital Discharge Data System (HDDS).

We selected the CRE surrogates by matching the risk score of 2,518 patients with CRE acquisitions with 638,583 inpatients in the 2018 HDDS. Patients were matched to achieve a 1:4 case-to-surrogate ratio without replacement, resulting in 10,069 CRE surrogates. Having multiple controls from the same population for each case increases the power of the study and precision of the effect sizes in epidemiological study. The noticeable increase in power, however, was only gained up to a control-to-case ratio of 1:4 (109) . We allowed for a caliper of 0.2 of the standard deviation of the risk score distribution and exact matches of age and sex.

Table 3.2 shows the breakdown of the demographic and selected clinical characteristics. CRE surrogates had similar risk score distribution with patients with reported CRE infections/

colonization, or CRE patients. Additionally, CRE surrogates have a comparable distribution of most characteristics used to generate the risk scores with CRE patients, including primary insurance, total LOS of previous stays at STACHs , previous inpatient hospitalizations, and DCCI score. Nevertheless, CRE surrogates have higher proportion of chronic lung disease than CRE patients (45.4% vs 37.3%, respectively), lower proportion of sepsis at index hospitalizations (19.8% vs 24.9%), lower proportion of urinary catheters presence in the previous 12 months (4.4% vs 9.6%). Furthermore, underlying conditions and healthcare exposures were more common among CRE surrogates than the general inpatient population. Other surrogate matching strategies, including using a threshold of risk score, or exact matching by individual characteristics that were predictive of hospitalizations, can result in a population with very similar risk profile with CRE patients. However, exploration of matching strategies was beyond the scope of the current analysis and future simulation studies can be used to address this issue.

Table 3.2 Characteristics of Patients with CRE Acquisitions, CRE Surrogates, and All Patients in Hospital Discharge Data

Patient Characteristics	Patients with CRE Infections/Colonization	CRE Surrogates	All Inpatients in HDDS
n	2,518	10,069	638,672
Female Sex (%)	1,563 (62.1)	5,431 (53.9)	369,164 (57.8)
Age (mean (SD))	64 (19)	59 (23)	47 (28)
Race and Ethnicity (%)			
Non-Hispanic White	1,840 (73.1)	7,719 (76.7)	473,839 (74.2)
Non-Hispanic Black	560 (22.2)	1,839 (18.3)	105,317 (16.5)
Hispanic/Other	107 (4.2)	365 (3.6)	38,101 (6.0)
Missing	11 (0.4)	146 (1.4)	21,415 (3.4)
Primary Insurance (%)			
Medicare/Medicaid	1,884 (74.8)	7,971 (79.2)	382,819 (59.9)
Commercial/Other	473 (18.8)	1,403 (13.9)	214,226 (33.5)
Uninsured	124 (4.9)	695 (6.9)	41,627 (6.5)
Missing	37 (1.5)	0 (0.0)	0 (0.0)
Re-admitted within 12 Months (%)	1,169 (46.4)	5,096 (50.6)	198,382 (31.1)
Sepsis during Index Hospitalization (%)	627 (24.9)	1,995 (19.8)	53,603 (8.4)
Healthcare Exposures within the Previous 12 Months**			
Inpatient Hospitalization(s) (%)	1,550 (61.6)	6,136 (60.9)	87,695 (13.7)
Total LOS at STACH, days (mean (SD))	35 (47)	37 (57)	21 (92)
Previous LTACH Stays (%)	133 (5.3)	80 (0.8)	610 (0.1)
Total LOS at LTACH, days (mean (SD))	81 (50)	58 (55)	62 (56)
Dialysis (%)	170 (6.8)	485 (4.8)	4,069 (0.6)
Urinary catheters (%)	241 (9.6)	442 (4.4)	2,297 (0.4)
Any Mechanical Ventilation (%)	261 (10.4)	480 (4.8)	4,197 (0.7)
Underlying Conditions			
Congestive Heart Failure (%)	855 (34.0)	3,459 (34.4)	85,025 (13.3)
Chronic Pulmonary Disease (%)	939 (37.3)	4,568 (45.4)	121,363 (19.0)
Renal Disease (%)	882 (35.0)	3,165 (31.4)	70,625 (11.1)
Diabetes (%)	849 (33.7)	1,651 (16.4)	32,725 (5.1)
Any Malignancy (%)	362 (14.4)	1,547 (15.4)	38,484 (6.0)
Charlson Comorbidity Index (mean (SD))	4 (3)	4 (3)	1 (2)

Abbreviations: SD, standard deviation; LOS, length of stay; STACHs, Short-Term Acute Care Hospitals; LTACHs, Long-Term Acute Cate Hospitals; SNF, skilled nursing facilities.

Note: Bolded patient characteristics were used to calculate the risk score to match CRE cases and surrogates.

*p-values were calculated using the Kruskal-Wallis test for continuous variables and Chi-square for categorical variables.

** Healthcare exposures were quantified within the previous 12 months of first specimen collection date for patients with CRE infections/colonization, and from the initial admission date of CRE surrogates and inpatient HDDS population.

$ The displayed median total Length of Stays at LTACHs and STACHs were calculated among patients with the previous LTACH and STACH stays only, respectively.

3.4 Network Data and Network Analysis

All transfers were quantified from the hospitalizations of patients who had their initial discharge in 2018 using the Tennessee Hospital Discharge Data System (HDDS) datasets from 2018 and 2019. HDDS is managed by The Tennessee Department of Health (TDH) Division of Population Health Assessment. It records one hospitalization per observation for all hospitalizations licensed by TDH. Veteran Affairs hospitals and other military hospitals were not included in HDDS. Patients who lived outside Tennessee but were treated in Tennessee hospitals are included, but their transfers to out-of-state hospitals cannot be captured.

3.4.1 Transfer definition

Transfers were classified as (1) direct transfer, defined as re-hospitalization at a different facility after the patient was discharged from another within one calendar day, and (2) indirect transfers, defined as re-hospitalization at a different facility after spending more than one day in the community. This study primarily assessed the PSN that aggregated indirect transfers within a 12-month intervening community stay based on the known duration of CRE colonization in the literature (section 1.2) (42,43,45,46,49).

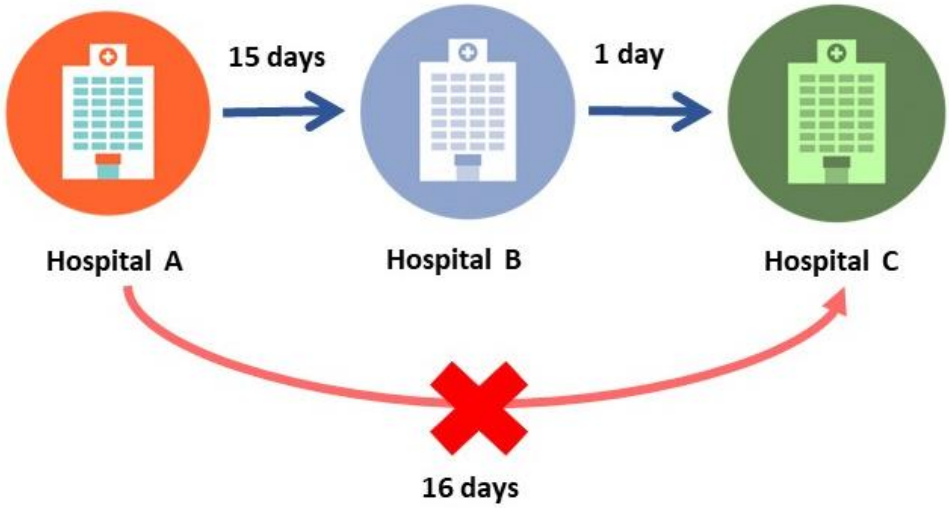


Figure 3.1 Illustration of hospitals connected by patient transfers

The re-admission of a patient to the same hospital as the discharging hospital was not considered a transfer. A patient who was discharged from hos pital A, re-admitted to hospital B, and later re-admitted to hospital C, would be represented in the network as transfers occurring from A to B and then from B to C, but not A to C (Figure 3.1).

The PSNs in this study included patients hospitalized in 2018 and re-admitted to another hospital within 12 months, including in 2019. Thus, we used the 2018–2019 HDDS dataset to construct the 2018 PSNs. To identify inpatient hospitalizations of the same individual, we linked their social security number and date of birth. If the patient's SSN was unavailable, the linkages were conducted using their first name, last name, and date of birth. In addition to exact matches, likely matches who had minor differences in patient identifiers were generated COMPGED and SPEDIS commands, which generated a score reflecting how similar the two strings of character were. As suggested by the SAS Software methodology publication, a likely or highly probably matches were best identified a threshold of 100 or lower for COMPGED and 10 for SPEDIS scores (110).

3.4.2 Network Dataset Construction

In hospital PSNs, a pair of consecutive hospitalizations of the same individual connects two hospitals, and all connections between hospitals form a PSN. The connection data in our study were organized into edgelists, which were datasets composed of at least three columns, including

(1) the sender hospital, the hospital that discharged the transferred patients

(2) the receiver hospital, which admitted the transferred patients, and

(3) the number of patients transferred from (1) to (2) in each period.

The edgelist recorded hospital pairs A and B as two data lines: the count of transfers from A to B and another for transfers from B to A. The number of aggregated one-way transfers for each hospital pair determined whether hospitals in columns (1) and (2) were connected in the patient sharing network. Hospitals were connected if there were at least one transfer between them or column (3) value was greater than zero.

3.4.3 Edge characteristics

Each hospital is represented as a vertex or a node. An edge is a connection between two hospital nodes, and the collective of edges and nodes interconnected to each other is called a network (111). The edge in the PSN has a direction, represented as arrows in a network diagram. The arrow originates at the discharging hospital and points towards the admitting hospital. Each arrow, or edge, is weighted by the number of patient transfers. Based on these network specifications, the PSNs in this study were classified as weighted and directed networks (88).

3.4.4 Node Characteristics

Each hospital had typical characteristics associated with increased in-hospital CRE prevalence, including its location in a high prevalence county, academic status, hospital type, number of beds, patient-days (the number of patients admitted to the hospital multiplied by the length of stays). Additionally, we calculated the node centrality measures of each hospital. Centrality measures are the various scores calculated from their position in the network to measure how central their role is in the network. Although there is a myriad of centrality measures used in network research, we only evaluated the most used and interpretable for epidemiologic studies, including

(1) indegree or the number of hospitals that send transfers into a given hospital,
(2) outdegree, the number of hospitals that receive transfers from a given hospital,
(3) weighted indegree, the number of patients transferred out from a given hospital,
(4) weighted outdegree, the number of patients transferred into a given hospital,
(5) betweenness, the number of times a hospital falls within the shortest path within the network diagram between other hospitals, and
(6) eigenvector, the measure of a hospital's importance in the network based on the importance of the hospitals it is connected to (111).

The centrality measures were assessed in the raw values and transformed if necessary to find the distribution that had the best model fit with the CRE prevalence. However, we also evaluated the transformed values or splines to assess if they provided a better model fit in an explanatory model that assessed their association with CRE prevalence.

3.4.4 Other Networks

To compare the surrogate network against other traditionally used networks, we constructed PSNs from the hospitalizations of patient populations used in published Multidrug-Resistant Organism (MDRO) studies. These populations included all inpatients in the hospital discharge dataset (90) and a subset of fee-for-service Medicare and Medicaid beneficiaries in HDDS (35). The hospitals in these networks were also connected through indirect transfers within 365 days in the same year as the CRE surrogate population. We compared the structure of these networks with a PSN constructed from the hospitalizations of patients identified with CRE infections in 2019. We linked the identifiers of the patients with CRE acquisitions with their hospitalizations in 2018 and re-hospitalizations within 12 months.

We analyzed the structure of each network, quantified the connectedness of each hospital within that network, and assessed the distribution of the centrality measures to the hospital's risk of exposure to CRE patients. The illustration of the network generation process is shown in Figure 3.2.

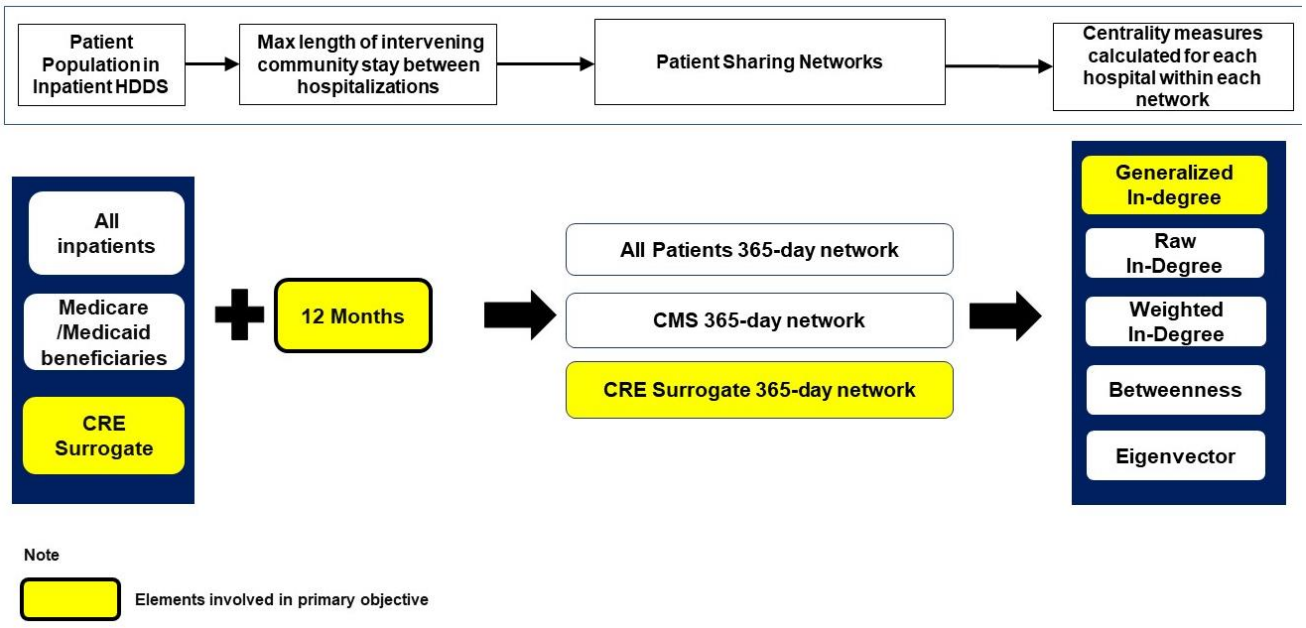


Figure 3.2 The illustration of network generation from patient transfer parameters and populations

3.5 Network structure comparison

We compared each generated network with the PSN generated from the actual hospitalizations of patients with CRE acquisitions in 2019. We hypothesized that the surrogate network should be the most similar network to the movement of identified patients with CRE infections. To assess this hypothesis, we looked at multiple ways of comparing networks, including:

(1) Observation of the network graph. The easiest way to compare networks was by drawing the network graph to visualize their structure and observe the key players. We drew all generated networks using the Fruchterman-Reingold graph layout. This force-directed graph layout used an algorithm to draw closely connected nodes towards the center of the network to minimize the energy used to visualize the system. This method aided us in identifying key players and clusters of highly connected hospitals within each PSN and provided initial inference of network comparisons (112). Additionally, we drew the network overlaying their geographical coordinates in Tennessee to show the location of highly connected facilities.

(2) **Comparison of edgelist distribution.** We conducted a Pearson correlation test to compare the number of transfers in the edgelists of PSNs from patients with CRE acquisitions with the edgelists of the networks from CRE surrogates, all inpatients, and Medicare and Medicaid beneficiaries. Our study included 144 hospitals; thus, edgelists were datasets with [144 *(144-1)] or 20,592 observations. We expected the Pearson correlation coefficient between the edgelists of CRE acquisitions and Surrogate networks to be higher than the other population networks.

3.6 Multivariable Explanatory Model

In the next step of the analysis, we addressed the primary objective of this study. To meet the study objectives of this aim, we evaluated each objective sequentially to compare the patient population, centrality measures, and generalized indegree α tuning value to follow the workflow in Figure 3.3. We evaluated the fit of the multivariable model using the surrogate network with a 12-month transfer period.

Table 3.3 Whole Network Characteristics to be Compared Between Networks

Network Characteristics	Definition
The number of nodes	The number of hospitals receiving or sending at least one transfer to another hospital within the network
The number of edges	The number of connections between hospitals that represent at least one transfer between hospital pairs
Density	The number of existing edges (connection) is divided by the number of possible edges within a network. For example, in a network of 144 hospitals, there are [144 * (144-1)] possible one-way edges between the hospitals (n edges=20,592)
Reciprocity	How often a transfer from hospital A to B is reciprocated by having at least one transfer between B and A
Diameter	The maximum number of hospitals serve as intermediates between two hospitals that were the furthest positioned relative to each other. This metric represents how many transfer events it could take for a pathogen in a hospital to reach the hospital's least connected to it
Mean Geodesic Distance	The average number of relations in the shortest possible paths from one hospital to another

Note: The definition of the network metrics is paraphrased from Jackson's Social and Economic Networks, First Edition(111).

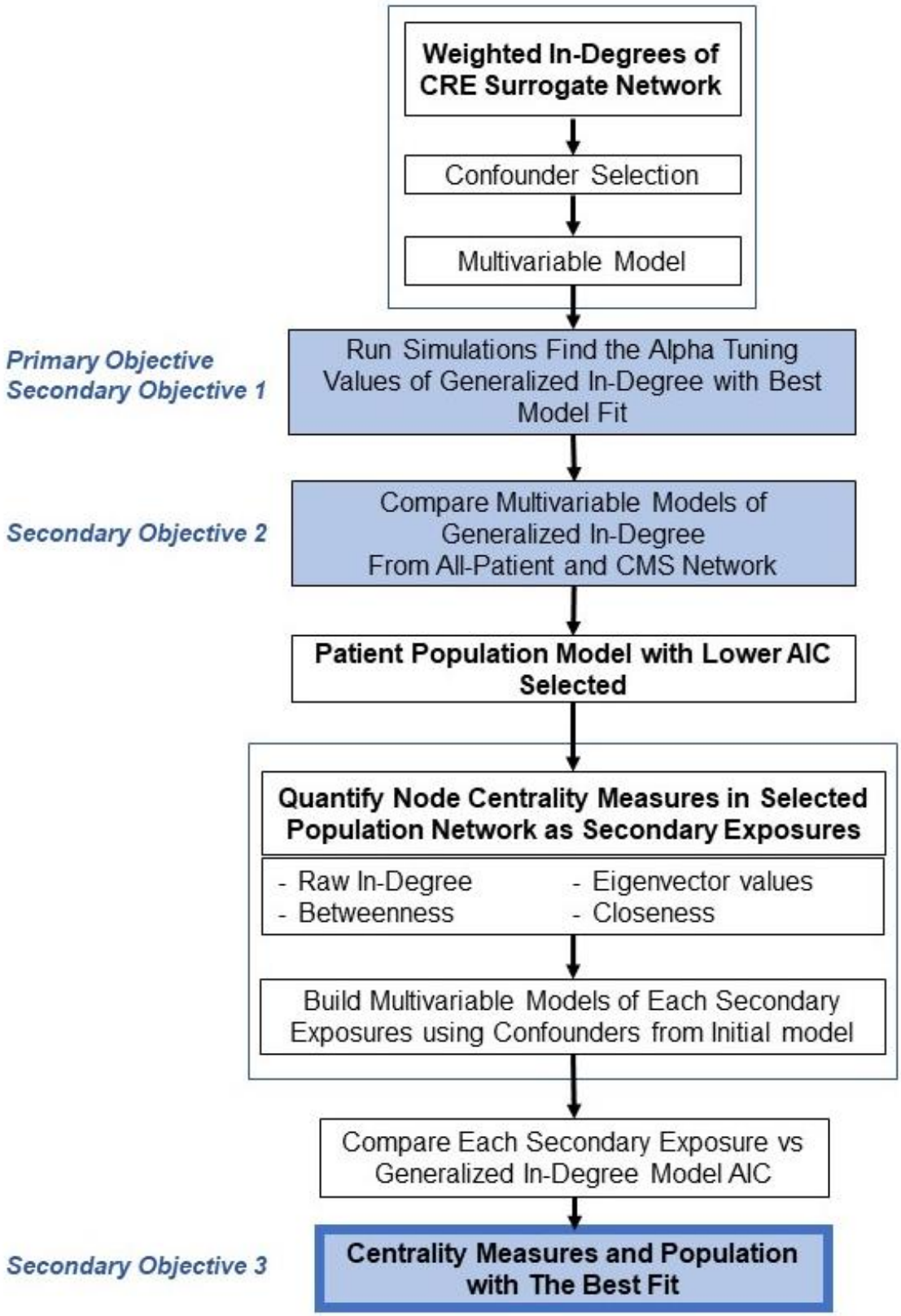


Figure 3.3 Stepwise Analytic Plan of the Second Study Aim

3.6.1 Primary Outcome

The primary study outcome was the prevalence of CRE events in each hospital in 2019, quantified by the number of CRE events per 1,000 patient-days. Patient-days was the total number of inpatient hospitalizations multiplied by their length of stay in 2019 and represented the hospital size and cumulative healthcare encounters. We considered each inpatient hospitalization during which the specimen was collected as a CRE event. If the patient was not hospitalized during specimen collection, we attributed a CRE event to the hospitalization that began within 14 days after the specimen collection (113). Alternatively, we attributed the specimen to the collecting hospital if the patient was not hospitalized. If multiple specimens were collected from the same patient in the same facilities within 14 days, only the first specimen was quantified. If there was a discrepancy between the lab reports and the HDDS, the information from HDDS was prioritized. We did not differentiate CRE events based on whether the patient had previous positive CRE specimens. Therefore, we did not quantify the incidence of CRE events in this study.

There were 929 CRE specimens from 731 patients reported to the Tennessee Department of Health in 2019. We attributed 721 (78%) of 929 specimens to at least one CRE event, representing 591 (81%) of all reported patients. We considered the remaining specimens collected at outpatient clinics or long-term care settings. In an epidemiologic study using surveillance data in seven geographical areas in the United States, 43% of CRE specimens were collected in outpatient settings or emergency departments, while 27% were in long-term care facilities (11). Our results suggested a satisfactory rate of facility matching that did not require us to do other quantification methods like residential ZIP Code matching.

3.6.2 Primary and Secondary Exposures

Additionally, we assessed the association between other centrality measures with CRE prevalence. The primary exposure of this analysis was the generalized indegree from the 12-month indirect transfer network of the CRE surrogate PSN from 2018. The primary exposure was measured 12 months before CRE prevalence was measured to mitigate the possibility of reverse causation. In separate models, we evaluated other centrality measures that have been reported to be associated with the risk of MDRO transmission or prevalence, including the raw indegree, raw outdegree, betweenness, eigenvector, closeness, weighted indegree, and weighted outdegree. The

effect sizes and precision of estimates from these traditional centrality measures were compared to the generalized indegree (114,115).

3.6.3 Multivariable Regression Model

The associations between each exposure and the CRE prevalence were evaluated using the multivariable regression model. The statistical model to assess prevalence outcome can be addressed by modeling a count response data, the number of CRE events in each hospital in 2019. The outcome has a mean of 4.5 and a variance of 106.8. Overdispersion is evident when the variance of the count data is significantly larger than the mean, which is observed in our data. The overdispersion of outcome data suggested that a negative binomial distribution model would better analyze the association between centrality measures and CRE prevalence.

Figure 3.4 shows the distribution of the number of CRE events in each hospital. Among 144 included hospitals, 71 (49%) did not report any CRE events, which means the distribution of the outcome is likely to have excess zeros as shown in Figure 3.4. A negative binomial model can be adjusted to improve model fit if there were excess zeros in the outcome distribution through a zero-inflated negative binomial (ZINB) model, generating two intercepts for zeros and non-zero counts (116). To assess the fit of negative binomial compared to ZINB models, we used the likelihood ratio tests and the Vuong test (117). A $p<0.05$ for either test indicated that the ZINB model provided additional information compared to the negative binomial model.

To allow the interpretation of effect sizes as a prevalence rate ratio, we included the offset term of the number of hospital patient-days in 2019. The patient-days for each hospital were the sum of the number of patients multiplied by their length of stay. Thus, 1,000 patient-days could mean 1,000 patients hospitalized for one day or one patient hospitalized for 1,000 days. The median patient-days of Tennessee hospitals in 2018 was 3,156 (IQR: 896–6,684). Thus, the patient-days were divided by 1,000 for simplicity.

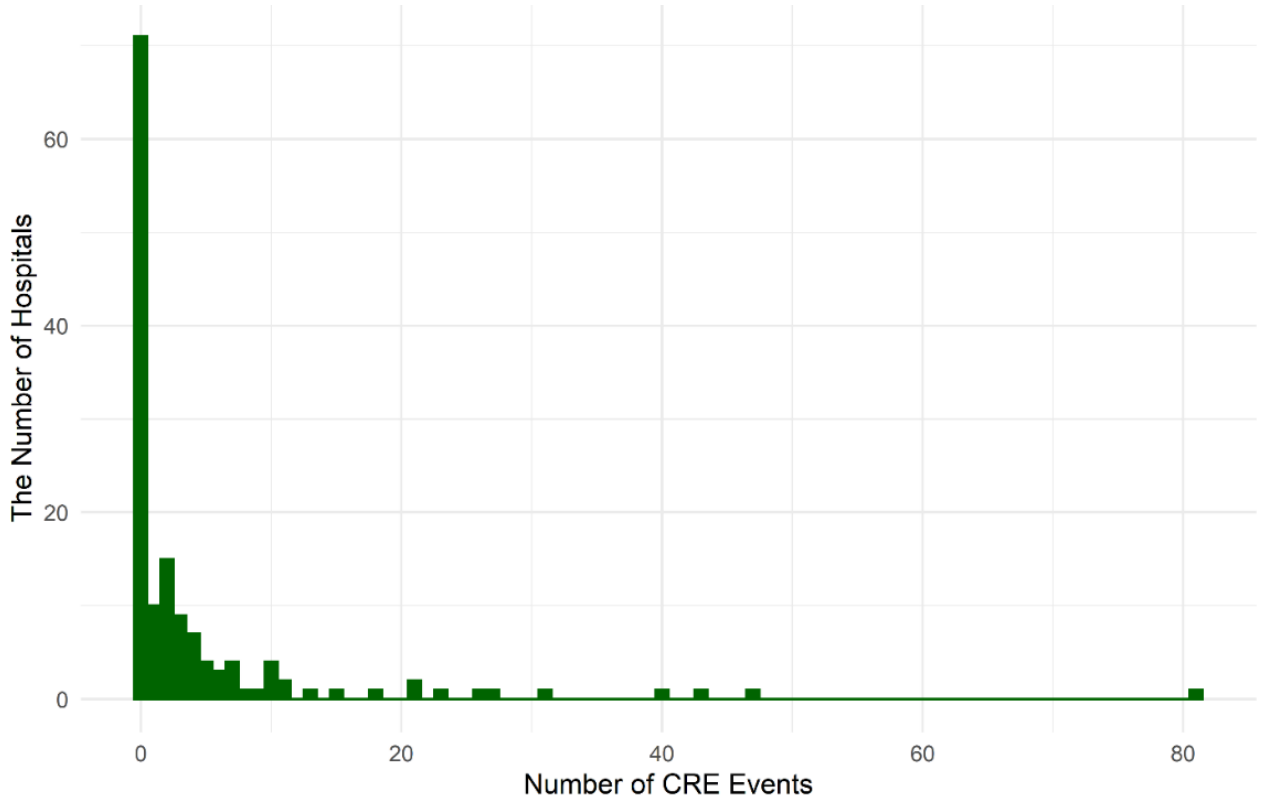


Figure 3.4 Histogram of The CRE Events per Hospital in Tennessee, 2019

Our model outcome was CRE prevalence, where patient-days is the denominator of response data λ (event) in its log form (λ /1,000 patient-days). The negative binomial regression modeled the parameter λ, the number of CRE events per unit of time or space in log (λ), with the following equation:

$$\log\left(\frac{\lambda}{1{,}000 \text{ patient-days}}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots \beta_n x_n$$

Which can be stated as well as :

$$\log(\lambda) - \log(1{,}000 \text{ patient-days}) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots \beta_n x_n$$

Thus, the regression equation used in our analysis was

$$\log(\lambda) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots \beta_n x_n + \log(1000 \text{ patient-days})$$

In this model, β_0 represents the intercept of the model, $x_1$the generalized indegree, β_1 the rate of increase of log(λ) for each one-unit increase in x_1. The confounders and the increase of log(λ) for each unit increase in confounders appear in the model as x_2 and β_2 and so on. Meanwhile, the patient-days was an offset term and its log-transformed value was included in the equation without a β value.

3.6.4 Variable transformation

We examined the crude look of the relationship between weighted indegree, or in other terms, generalized indegree with an α of 1, and the log prevalence (CRE events/1000 patient-days). Data transformations were used to handle potential model assumption violations to improve the model fit. A model with a good fit would show a linear relationship between the exposure and the log-transformed outcome. In the initial examination, we found that a base-two logarithmic transformation of weighted indegree was the most appropriate for the model. With a log-transformed negative binomial model with an offset term, a $\log_2$-transformed exposure allowed us to interpret the effect size as the increase in hospital-level CRE prevalence for each doubling of the exposure. We compared the multivariable models that used weighted indegree and $\log_2$-weighted indegree as primary exposure using Akaike Information Criterion (AIC) values and residual plots. The model with $\log_2$-weighted indegree had a lower AIC and randomly distributed residuals, suggesting a superior fit. Similarly, we evaluated spline terms for $\log_2$-weighted indegree by comparing the model without and with three-knots spline terms.

3.6.5 Confounder Selection

We used a directed acyclic graph (DAG) to illustrate the causal relationship between hospital centrality measures (including primary and secondary exposures) and CRE prevalence in the following year. Hospital-level covariates were included as potential confounders based on *a priori* knowledge of the risk factors of increased CRE prevalence and hospital (Section 1.5) and inputs from subject matter experts. The DAG also helped us select the minimum set of confounders sufficient to control for confounding bias in the association between the exposure and the outcome.

We also evaluated whether adding each potential confounder into a model with only weighted indegree and the CRE prevalence resulted in a 10% change in the coefficient (β estimates) of weighted indegree. This method, called the 10% change-of-estimate method, is often

used in conjunction with the DAG method to evaluate additional covariates. Our evaluation did not result in any additional covariate being included. Weng *et al.* conducted a simulation to assess the model performance, evaluated from metrics of bias and precision, between different confounder selection processes. Their simulation showed that the DAG-only method without a 10% change-in-estimate method resulted in an explanatory model with comparable or better performance than the model that included confounders with both methods, even when true confounders were omitted from the DAG (118).

We evaluated seven hospital-level potential confounders, including hospital type, academic or teaching status, urban location, hospital-level infection prevention activities, hospital size, CRE prevalence in the previous year, and the proportion of transfers from Long-Term Acute Care Hospitals (LTACHs). Hospital-level infection prevention activities can be evaluated using the Infection Control Assessment and Response (ICAR) Tools published by the CDC to systematically assess the healthcare facility's infection control practices and address the identified gaps (119). TDH has performed ICAR assessments, but this information was not collected in our dataset, and thus considered unmeasured potential confounder. Infection control prevention activities were included in the DAG to assess the level of information loss by not including this confounder to estimate the total effect of centrality measures to CRE prevalence. The DAG in Figure 3.5 suggested that the minimum sufficient set of confounders to include in the multivariable model measured hospital size, facility type, academic affiliation, and urban location. Thus, a measure of infection prevention activities can be omitted from the multivariable model. The measure of hospital size was represented by the patient-days, which we had included as an offset term. Based on their licensure information, we categorized facility types into LTACHs and short-term hospitals. Short-term hospitals included acute care hospitals, critical access hospitals, and inpatient rehabilitation hospitals. We defined urban hospitals as those located in an urbanized city with a population of 50,000 or more according to the US Census Bureau designation and 2020 U.S. Census data and designation by the State of Tennessee (120). The initial descriptive analysis of the covariates from the surrogate network is shown in Table 3.2.

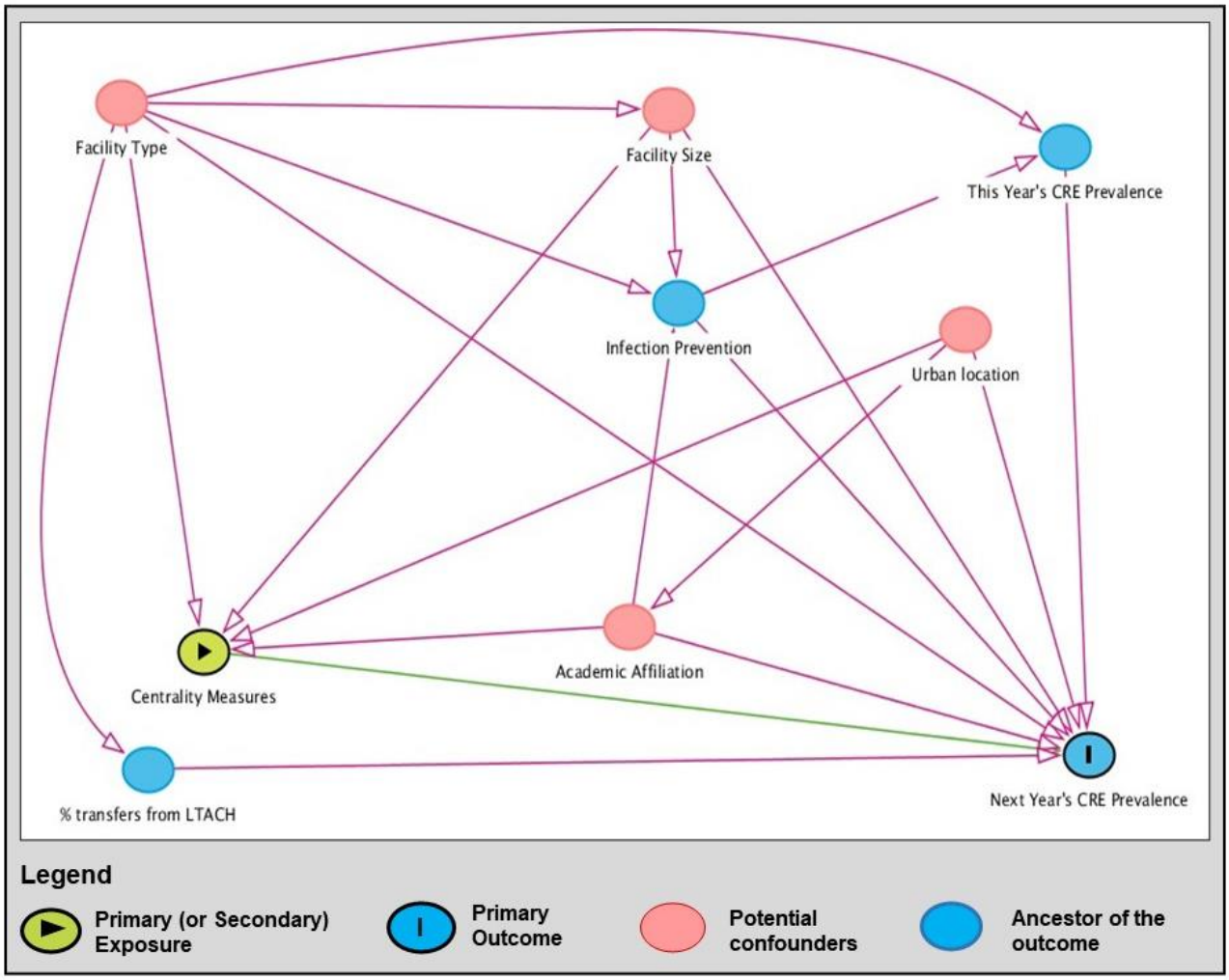


Figure 3.5 Causal Diagram of The Relationship Between Generalized Indegree and CRE Prevalence

Note: Each node in the figure represents a hospital-level characteristics involved in the causal relationship between the centrality measures (primary exposure) and the CRE prevalence in the following year (primary outcome). The arrow represent the direction of the causality between each characteristics.

3.6.6 Effect modification

LTACHs were disproportionately burdened by CRE compared to short-term acute care hospitals (86,90). LTACH patients had more prolonged hospitalizations and commonly had underlying conditions. Receiving transfers from LTACHs was known to increase other hospitals'

risk of encountering CRE patients (90). Therefore, we evaluated two potential effect measure modifiers (EMMs), including LTACH facility type and the proportion of transfers from LTACH for their interactions with generalized indegree. We evaluated each EMM using the negative binomial regression model with the number of CRE events, generalized indegree with an α=1, or weighted indegree, the potential EMM, and the product of the interaction term EMM and generalized indegree. We considered a p-value of <0.20 of the interaction term to include the EMM in the final multivariable model.

3.6.7 Estimation of Generalized Indegree

We evaluated novel measures that combined the number of hospitals and the magnitude of incoming transfers into generalized indegree. A similar measure of generalized outdegree quantifies the number and magnitude of outgoing transfers. These centrality measures were proposed by Opahsl (121) to represent connectedness in a weighted directed network. In both measures, *k* was the number of hospitals that transferred patients in (or out) of a given hospital (indegree), and *s* represented the number of patients transferred to and from a given hospital (weighted indegree). Opahsl's generalized indegree and outdegree for each hospital (*i*) were calculated as

$$generalized\ indegree(i) = k_i^{in} * [\left(\frac{s_i^{in}}{k_i^{in}}\right)^{\alpha}] \quad (3.1a)$$

$$generalized\ outdegree(i) = k_i^{out} * [\left(\frac{s_i^{out}}{k_i^{out}}\right)^{\alpha}] \quad (3.1b)$$

To tune the combination between degree and strength of ties, Opahsl used a tuning parameter α, which determined the relative importance of the number of hospitals compared to the number of patients. If α were between 0 and 1, then the number of hospitals was considered more favorable to quantify how central the role of each hospital is in the network. At the same time, if the α were greater than 1, the number of patients was taken more positively. A value of α=0 means only the count of hospitals influenced the generalized indegree or an equal value to indegree. Meanwhile, α=1 meant only the number of patients influenced the generalized indegree.

There were no previous studies that used generalized degrees in PSN research. Therefore, there was no prior distribution to start a Bayesian model or a known α value besides 0 and 1 used

to begin tuning the α for generalized indegree that incorporate both metrics. To tune the α value with the best fit to the data, we simulated the multivariable Poisson model using multiple α values. The main predictor of these regressions was the generalized indegree against the outcome of CRE prevalence, adjusted by confounders from the causal diagram in the multivariable explanatory model. Each regression used generalized indegree in varying α levels to output the β value, 95% confidence interval, and model fit using Akaike Information Criterion (AIC). The generalized indegree α value preferably has a high β (strong association), narrow confidence interval (high precision), and low AIC (better model fit).

3.6.8 Sample Size and Power

The subjects of our study were 144 hospitals in Tennessee. Negative binomial models' estimates were interpreted as prevalence rate ratios, which indicates the change in prevalence associated with the increase of primary exposure. A previous study found an increase of 1 in log weighted indegree associated with a 3.3% increase in *C. difficile* incidence, another type of MDRO infection. In contrast, another study found that an increase of one raw indegree caused a 6% increase in the CRE rate in rural areas and a 3% increase in urban areas(90). We measured the study power for CRE with an expected PRR of 1.03–1.70 to represent small to moderate effect sizes. Based on a hospital-based prevalence study conducted in 2018, the incidence of CRE in hospitals was approximately 3.23–3.79 events per 10,000 hospitalizations, with no change in trends expected in 5 years. We chose the higher incidence level to measure study power.

The study power was estimated in Stata 16 (StataCorp, College Station, Texas) using an exponential model that compares the rates of outcome between two groups. Although our primary exposure was a continuous variable, the study power was estimated using three potential ratios between highly connected to less connected hospitals. From these estimations, the study power of a model with 144 hospitals with 5% type 1 error was ≥80% with a 1:1 ratio of two groups for a rate ratio of 1.58 or higher and 1.63 for a 2:1 ratio. The power curve is shown in Figure 3.6.

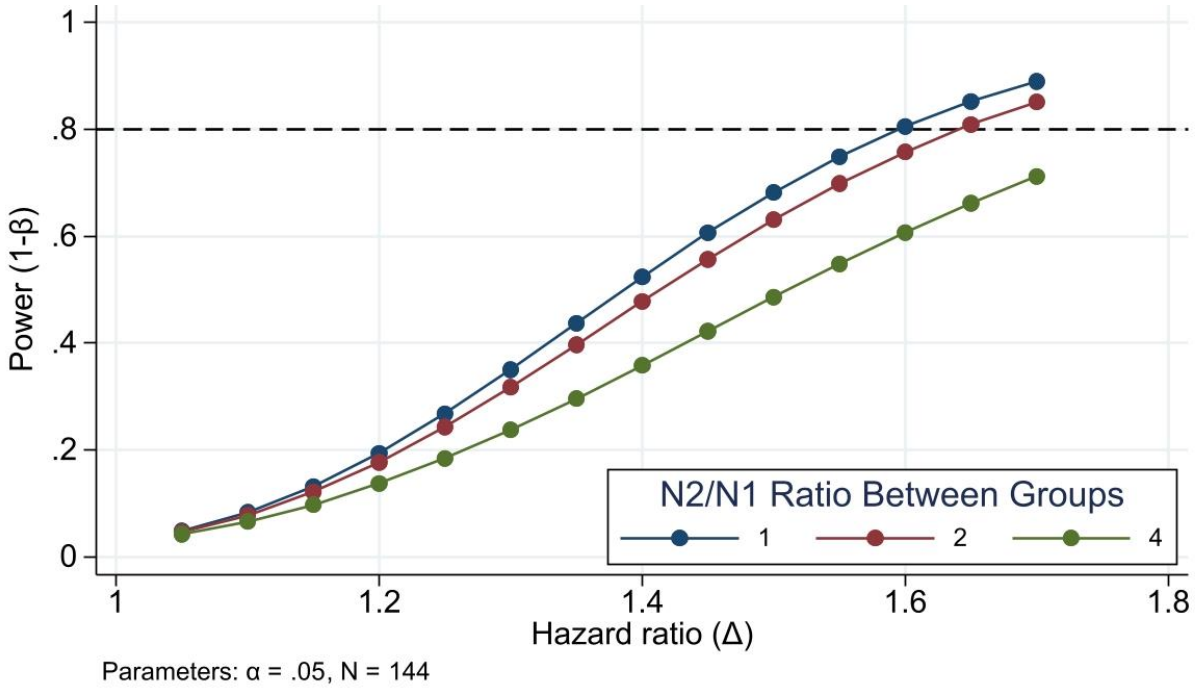


Figure 3.6 Sample Size and Power Curve for Rate Ratio Calculation

3.7 Study Results

3.7.1 Network Analysis Results

The patient sharing network (PSN) generated from the transfers of CRE surrogates, referred to as the surrogate network, included 141 (98%) of 144 Tennessee hospitals. This network was constructed from the hospitalization patterns of 10,071 patients with similar characteristics to CRE patients. We also constructed a PSN from the transfers of all inpatients (n=638,583) in the HDDS dataset, henceforth referred to as an all-patient network. Similarly, we constructed a network from 294,639 Medicare and Medicaid beneficiaries in the HDDS inpatient dataset, referred to as the CMS network. The PSN constructed from the transfers of patients with CRE acquisitions, henceforth referred to as the CRE patient network, only connected 109 of 144 (76%) hospitals. We linked the hospitalizations of 641 (88%) out of 731 patients with positive CRE specimens in 2019.

Table 3.4 compares the whole network characteristics of the PSNs in this study. The structures and network statistics of the surrogate, all-patient, and CMS networks were compared against the CRE patient network to assess their suitability for estimating hospital-level risks of CRE transmissions. The all-patient and CMS network characteristics differed from the surrogate and CRE patient networks. In all networks, the connections of most hospital pairs were reciprocal, meaning they both transferred patients to and from each other. The highest reciprocity was observed in the CRE patient network and similarly in the Surrogate network.

Table 3.4 Whole Network Statistics Comparisons

Network Characteristics	All Patients	Medicare/Medicaid Beneficiaries	CRE Surrogates	CRE Patients
Number of Patients	638,583	294,639	10,043	641
Number of Transfers	11816	4204	1315	401
Number of Hospitals	144	143	141	109
Network Density	0.57	0.21	0.07	0.03
Reciprocity	0.81	0.89	0.96	0.97
Mean Geodesic Distance	1.42	1.85	NA	NA
Network Diameter	3	4	5	8
ρ (95% CI)	0.55 (0.54, 0.56)	0.61 (0.6, 0.62)	0.60 (0.59, 0.62)	NA

Abbreviations: CRE, Carbapenem-Resistant Enterobacterales; 95% CI, 95% Confidence interval.
Note: Network characteristics were calculated using the *'statnet'* package in R specified for weighted directed networks.
*The correlation coefficients (ρ) and 95% confidence interval between the edgelists from all-patient, Medicare/ Medicaid, and Surrogate networks against the CRE patient network were calculated using the Pearson correlation test.

We quantified the average number of relations in the shortest possible walks from one hospital to all other hospitals, known as geodesic distance. The concept of geodesic distance can be illustrated through the transmission of a hypothetical pathogen from hospital A to hospital C within a network. Initially, the pathogen was transmitted from hospital A to hospital B because they were linked through patient transfers (path length of one). Later, hospital B sent transfers to hospital C, and the pathogen was transmitted to hospital C (path length of two). In this scenario, the pathogen reaches C from A through two walks or two geodesic distances. The average geodesic distances were 1.42 in the all-patient PSN and 1.85 in the CMS network, suggesting that the pathogen could hypothetically reach any other hospital in less than two walks. Because not all hospitals were connected within the surrogate and CRE patient PSNs, the geodesic distances cannot be calculated as a comparative statistic against the all-patient or CMS networks.

Figure 3.7 shows the geographical representation of eight Tennessee Emergency Medical Services (EMS) Regions and Figure 3.8 shows the network diagram of patient sharing networks drawn using the Fruchterman-Reingold layout. The colors of the nodes (hospitals) in the network diagram in Figure 3.8 corresponded to the EMS regions. Additionally, the geographical representation of the patient sharing networks were shown in Figure 3.9. The all-patient network in Figure 3.8(a) and Figure 3.9(a) shows an unclear pattern of connectedness and key players within this network. The density of the all-patient network is 0.57, meaning that out of 20,592 possible connections between 144 hospitals in the network, 11,737 (57%) were connected by at least one transfer. All other networks had a lower density, with the CRE patient network having the lowest density. A network with a high density is usually more homogeneous, meaning that it is more challenging to identify clustering patterns or important players or facilities (111). The structure of the CRE patient network in Figure 3.8(d) was noticeably different from the all-patient network and had a more similar clustering pattern to the CMS network and surrogate network.

The patient sharing networks were generated from the transfers of inpatients in the 2018–2019 Because not all hospitals were connected within the surrogate and identified CRE patients PSNs, the geodesic distances cannot be calculated as a comparative statistic against the all-patient or CMS networks.

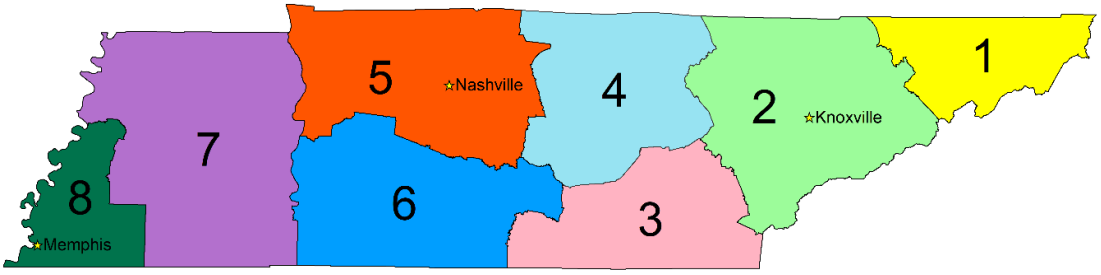


Figure 3.7 The Map of Tennessee Emergency Medical Services Regions

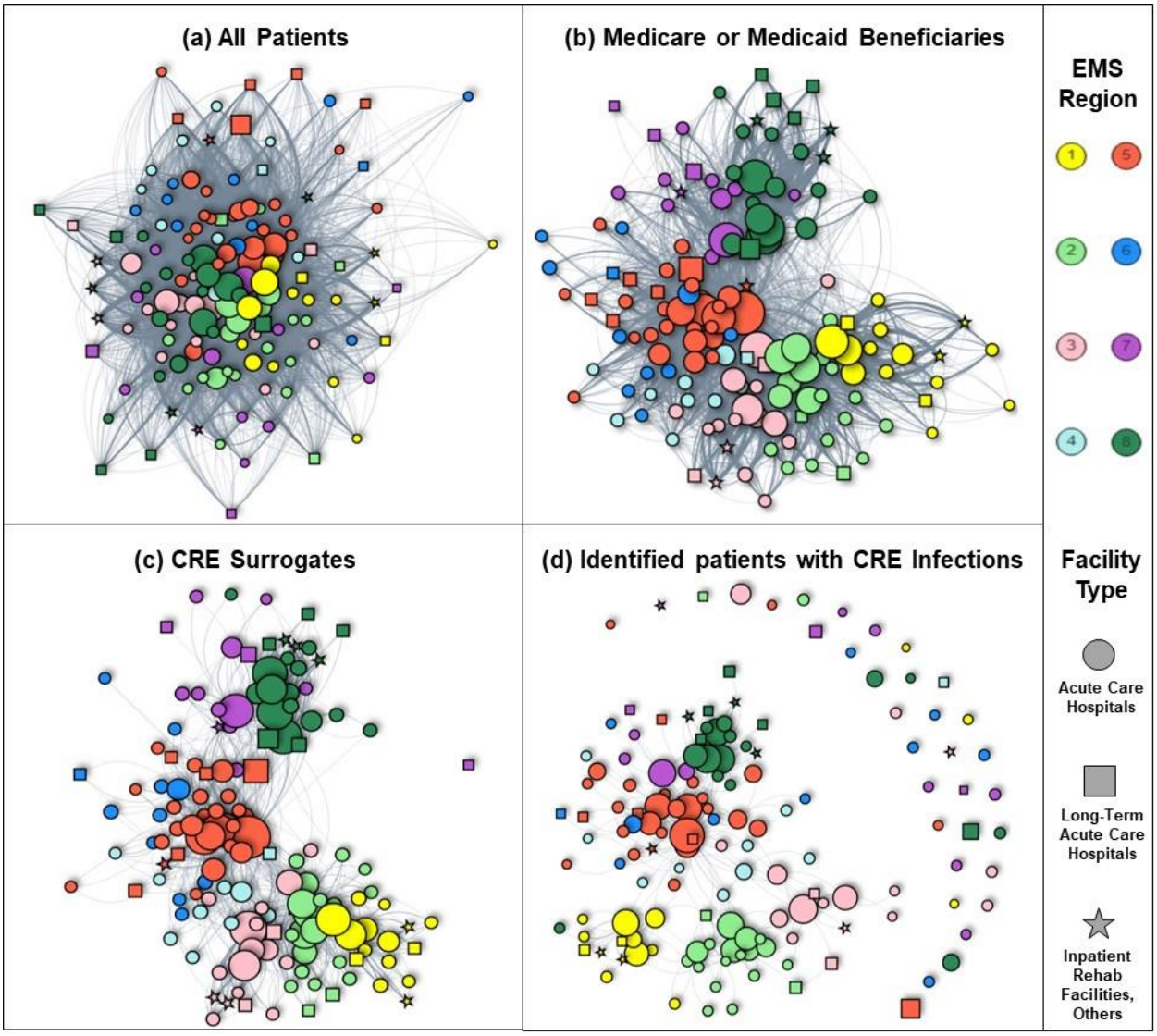


Figure 3.8 The Structural Comparison of 2018 Patient Sharing Network Diagrams from the Hospitalization of Various Patient Populations

Note: Hospital Discharge Data within 12 months, including (a) All patients, (b) Fee-for-services Medicare and Medicaid beneficiaries, (c) CRE Surrogates, and (d) Identified patients with CRE infections. Each node represents one hospital, and the thickness of the connections between nodes represent the magnitude of patient transfers. The color of the nodes corresponds to the Emergency Medical Services (EMS) regions where the hospital was located. The shape of the nodes represents the facility types. The network diagrams were drawn using the Fruchterman-Reingold algorithm.

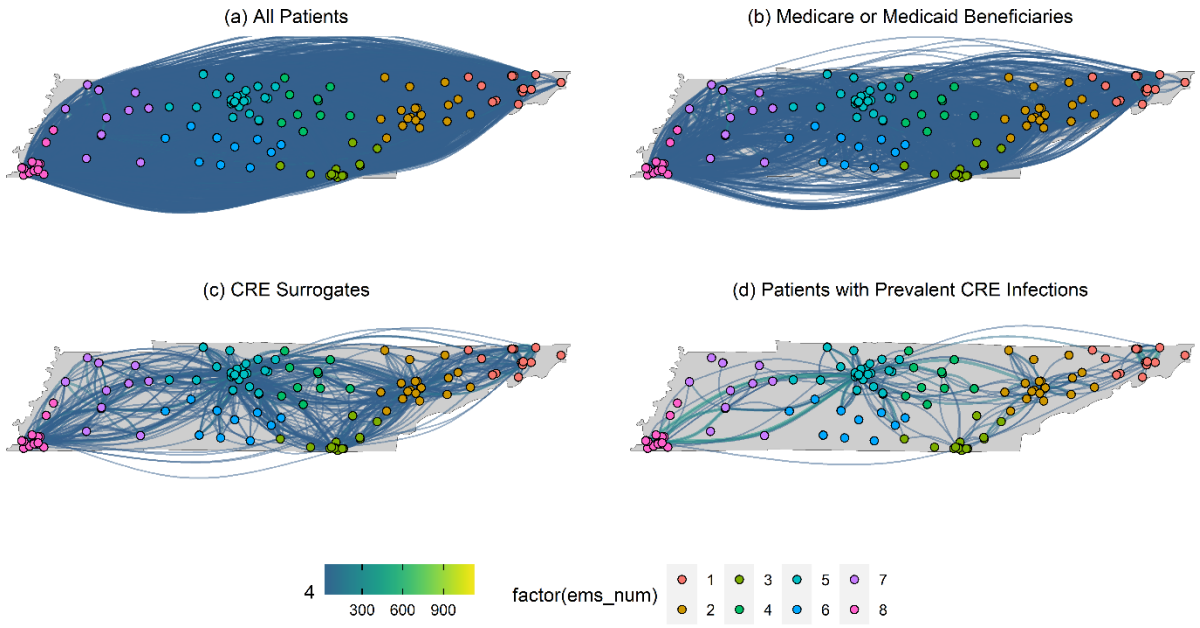


Figure 3.9 Geographical Representation of the Tennessee Patient Sharing Network
Note: The patient sharing networks were generated from the transfers of inpatients in the 2018–2019 Hospital Discharge Data within 12 months, including (a) All patients, (b) Fee-for-services Medicare and Medicaid beneficiaries, (c) CRE Surrogates, and (d) Patients with CRE acquisitions. Each node represents one hospital, and the color of the connections between nodes represents the magnitude of patient transfers. The color of the nodes corresponds to the Emergency Medical Services (EMS) regions where the hospital was located.

Figure 3.8 (b-d) allowed us to compare the structures of the CMS, CRE surrogates, and CRE patient networks. The CMS network had a lower density than the HDDS network. Furthermore, the CMS network showed apparent clustering of hospitals by their Emergency Medical Services (EMS) region. This clustering and network structures CMS network were comparable to that of the surrogate network (Figure 3.8(c)) and CRE patient network (Figure 3.8 (d)), which were constructed from the transfers of fewer patients. Nevertheless, the tie strength

between these hospitals was less robust due to fewer transfers in CRE surrogate and actual CRE patient PSNs.

The network's key players were drawn in the center of a network graph with a force-directed layout like the Fruchterman-Reingold layout. Large acute care hospitals in Emergency Medical Services (EMS) region 5, which represented the Nashville Metropolitan Area, were drawn in the center of the graph in the CMS, CRE surrogate, and CRE patient networks. We also observed that the facilities located in EMS regions adjacent to each other were more connected than those in EMS regions that were geographically further. The central positioning of hospitals in EMS region 5 in the network graphs suggested that hospitals in this region were connected to hospitals in many other regions(122). This finding is expected from the geographical positioning of this region, where many teaching hospitals or other centers offering more complex surgical procedures are located.

The CRE patient network only connected 109 (76%) of 144 hospitals in Tennessee, as shown in the remaining isolated hospitals at the right pane of **Figure 3.8**(d). Nevertheless, the key players and clustering patterns in the CRE network were comparable to the surrogate network and, to a lesser extent, the CMS network. Furthermore, the CRE patient network had a moderate correlation with the surrogate network (Pearson ρ=0.60, 95% CI: 0.59, 0.62), and to slightly higher extent to the CMS network (ρ=0.61, 95% CI: 0.60, 0.62). The correlation was lower between CRE patients and all-patient networks (ρ=0.55, 95% CI: 0.54,0.56). Although the correlation coefficient between the surrogate network with CRE patient network was slightly lower than that of the CMS networks, the surrogate network has more similar structure and other characteristics to CRE patient network. Therefore, we used the centrality measures from the surrogate network to evaluate the association between hospital connectedness and CRE prevalence in the next step.

3.7.2 Explanatory Model Results

The characteristics of hospitals included in the multivariable regression model are listed in Table 3.5. Among 144 hospitals included in the analysis, 73 (51%) reported CRE events in 2019. The mean number of CRE events was 4.5 (SD=10.3), with a mean rate of 0.12 (SD =0.25) events

per 1,000 patient-days. All LTACHs (n=8) in our study reported CRE events in 2019. Hospitals with CRE events were more likely to be located in urban areas, had academic affiliations, and had higher patient-days (all $p<0.05$). All evaluated centrality measures were significantly higher among hospitals with CRE events(all $p<0.001$).

Observation of the distribution of centrality measures and its association with the CRE prevalence suggested that a log transformation of the centrality measures is necessary to fit a negative binomial model to produce a linear relationship between the exposure and outcome at the log scale. A base-two log transformation was selected for centrality measures for the interpretability of the effect sizes. The prevalence rate ratio from the base-two log transformation can be interpreted as the change in the rate of CRE events for each doubling of the centrality measures(123,124). The multivariable regression model included the $\log_2$-transformed centrality measures and three confounders, including urban location, academic affiliation, and whether the hospital was a Long-Term Acute Care hospital (LTACH). No evidence of statistical interaction (interaction term p-value=0.991) was observed between LTACH hospital type and $\log_2$-weighted indegree or $\log_2$-generalized. The Vuong test suggested that the zero-inflated negative binomial model did not provide additional information or improved model fit compared to the negative binomial model ($p=0.286$).

Table 3.5 Hospital General Characteristics and Centrality Measures of the 12-month Surrogate Network

	Having >=1 CRE Events in 2019			
Hospital Characteristics	No	Yes	p-value	Overall
n	71	73		144
Facility type (%)			<0.001	
Acute care hospitals	40 (56.3)	61 (83.6)		101 (70.1)
Long-term acute care hospitals	0 (0.0)	8 (11.0)		8 (5.6)
Inpatient rehabilitation facility	6 (8.5)	3 (4.1)		9 (6.2)
Critical access hospitals	11 (15.5)	1 (1.4)		12 (8.3)
Psychiatric hospitals	14 (19.7)	0 (0.0)		14 (9.7)
Total patients-days in 2019 (mean (SD))	11,458.9 (14478.8)	50330.7 (58804.5)	<0.001	31164.7 (47,159.5)
N Hospitalizations, 2019 (mean (SD))	18,56.3 (2061.0)	9,870.9 (10652.7)	<0.001	5919.3 (8,682.4)
Number of Beds (mean (SD))	91.8 (72.5)	249.1 (225.8)	<0.001	171.6 (185.7)
Average length of stay (mean (SD))	7.7 (10.8)	7.5 (7.4)	0.904	7.6 (9.2)
High prevalence county location (%)	9 (12.7)	17 (23.3)	0.150	26 (18.1)
Urban location (%)	22 (31.0)	42 (57.5)	0.002	64 (44.4)
Teaching Hospital (%)	4 (5.6)	16 (21.9)	0.010	20 (13.9)
Centrality measures(mean(SD))				
Raw in-degree	5.4 (4.0)	13.7 (10.5)	<0.001	9.6 (9.0)
Weighted in-degree	12.5 (12.0)	53.4 (50.4)	<0.001	33.3 (42.1)
Generalized In-Degree, alpha=.5	8.0 (6.6)	26.6 (22.4)	<0.001	17.4 (19.0)
Raw out-degree	5.6 (3.9)	13.5 (10.8)	<0.001	9.6 (9.1)
Weighted out-degree	13.3 (12.4)	53.2 (51.8)	<0.001	33.5 (42.8)
Betweenness	54.8 (94.3)	478.4 (1030.8)	0.001	274.1 (771.9)
Eigenvector values	0.0 (0.0)	0.1 (0.1)	<0.001	0.1 (0.1)

*Patient-days is the sum of all hospitalization lengths of stays in the hospital within a year.
Categorical variables were displayed as count (%), and categorical variables were displayed as mean (standard deviation).
P-values between groups were calculated using t-test for continuous variables and chi-square test for categorical variables.

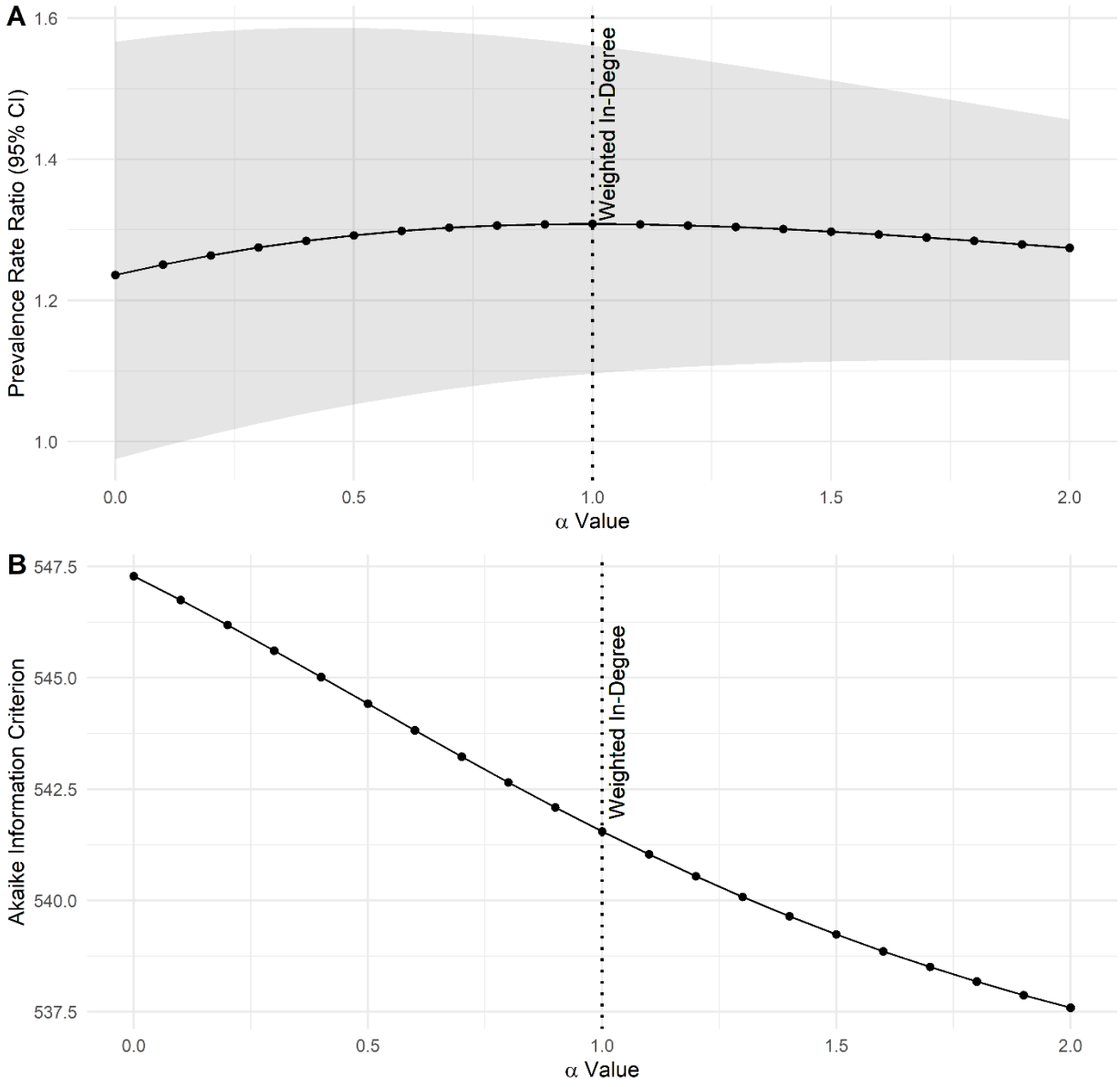


Figure 3.10 Generalized Indegree α Value Simulation Results

Figure 3.10 shows the simulation results for log_2 -generalized indegree across levels of α values (range 0-3) . The highest prevalence rate ratio (PRR) for log_2-generalized indegree was 1.33 (95% CI: 1.13, 1.59) at α=1, which is simply the equivalent of weighted indegree. This α level also had lower AIC score than the AIC scores from the models with generalized indegrees with α < 1, which suggested a superior model fit. The AIC values decreases as α increases. Nevertheless, the PRR of log2-generalized indegree for α >1 was challenging to interpret in applied public health practice.

Table 3.6 shows the comparisons of prevalence rate ratios and model fit of weighted indegree between different patient sharing networks. Each adjusted prevalence ratio was estimated using separate multivariable models, adjusted for urban location, long-term acute care hospital type, and academic affiliation. The PRR of log_2-weighted indegree was highest for CRE surrogate network compared to all-patient and CMS network. Additionally, the AIC values of the model with weighted indegree were lower for the CRE surrogate network models than for all-patient and CMS networks. Based on the model fit, the centrality measures from the surrogate network had a better fit and strongest association with CRE prevalence compared to other population networks.

Table 3.6 Comparisons of Prevalence Rate Ratio Between Patient Sharing Networks

Patient Populations	Prevalence Rate Ratio (95% CI)		Multivariable Model AIC
	Crude	Adjusted	
Log_2-Weighted Indegree (α=1)			
CRE Surrogates	1.14 (0.99, 1.34)	1.33 (1.13, 1.59)*	542.51
All Patients	1.06 (0.94, 1.21)	1.27 (1.08, 1.51)*	545.02
Medicare / Medicaid Patients	1.06 (0.92, 1.23)	1.21 (1.02, 1.44)*	548.75

Abbreviations: AIC, Akaike Information Criterion; CI, Confidence Interval; CRE, Carbapenem-Resistant Enterobacterales.
*Wald $p<0.05$ of the centrality measures
Note: All adjusted prevalence rate ratios were estimated using a multivariable model adjusted for urban location, long-term acute care hospital type, and teaching status. The model used an offset of log 1,000 patient-days.

We also compared some commonly used centrality measures and CRE prevalence within the surrogate network in Table 3.7. The PRR for log_2 weighted indegree in surrogate network can

be interpreted as an increase of CRE prevalence by 33% (95% CI: 33%, 59%) for each doubling of incoming transfers of patients with similar characteristics to CRE patients.

Table 3.7 Comparisons of Prevalence Rate Ratios Between Centrality Measures in the Surrogate Network

Log_2-Transformed Centrality Measures	Prevalence Rate Ratio (95% CI)		Multivariable Model AIC
	Crude	Adjusted	
Weighted In-Degree	1.14 (0.99, 1.34)	1.33 (1.13, 1.59)*	542.51
In-Degree	1.15 (0.92, 1.44)	1.28 (1.02, 1.61)*	548.89
Weighted Out-Degree	1.12 (0.96, 1.32)	1.24 (1.05, 1.48)*	547.40
Out-Degree	1.06 (0.85, 1.34)	1.18 (0.94, 1.50)	551.44
Betweenness	1.00 (0.94, 1.08)	1.06 (0.98, 1.15)	549.66
Eigenvector	0.72 (0.04, 20)	3.22 (0.13, 113.23)	551.20

Abbreviations: AIC, Akaike Information Criterion; CI, Confidence Interval; CRE, Carbapenem-Resistant Enterobacterales.

*Wald $p<0.05$ of the centrality measures

Note: All adjusted prevalence rate ratios were estimated using a multivariable model adjusted for urban location, long-term acute care hospital type, and academic affiliation. The model used an offset of log 1,000 patient-days.

3.8 Discussion

Our study results showed that generalized indegree, which combined the number of transfers and hospitals that sends incoming transfers, was associated with the prevalence of CRE. We also found that the patient sharing network generated from the interfacility transfers of CRE surrogates was correlated with the transfers of patients with reported prevalent CRE infection and colonization. The centrality measures from the surrogate network had a stronger correlation and resulted in a model with a better fit with CRE prevalence than all-patient and CMS networks.

The surrogates were generated using a case-control matching process on age, sex, and risk scores for re-admissions. The same matching process is commonly used in epidemiological studies and can be easily replicated in other datasets. The use of CRE surrogates in ARO studies has been

demonstrated by Wolford *et al.*'s with networks constructed using New York's Statewide Planning and Research Cooperative System (SPARCS) (125). In their study, the CRE surrogates were selected from 26,009 hospitalized patients as surrogates from 1,954 CRE cases. These surrogates had the following hospitalization characteristics: (1) length of stay of $\geq$14 days, (2) sepsis diagnosis, (3) and at least one underlying comorbidity or healthcare exposure, including adult respiratory failure, acute renal failure, or procedure/device complication. The PSN generated from the transfers of CRE surrogates was highly correlated (R=0.81) with the PSN from hospitalized CRE-infected patients. Our study showed a lower correlation between surrogates and the CRE patient network (R=0.63), which may be explained by the broader inclusion of CRE patients in our analysis to include non-hospitalized patients. These patients may have their CRE specimens collected in outpatient clinics and long-term care facilities. Only including hospitalized patients with CRE acquisitions may exclude patients with less severe infections or clinical conditions.

We also showed that the model with $\log_2$-weighted indegree, the equivalent of generalized indegree with α=1, had a better fit than the models with lower α values. Additionally, the PRR of $\log_2$-weighted indegree was more interpretable for practical risk assessment in regional infection prevention. The prevalence rate ratio of $\log_2$-weighted indegree means that as the number of incoming transfers of patients with similar characteristics to CRE patients doubled, the prevalence of CRE acquisitions increased by 33% in the following year(123). This study's use of log2 transformation was initially performed for statistical purposes due to the highly skewed distribution of centrality measures among Tennessee hospitals (Figure 3.11). However, it also provided a better relevance to the hospital populations in the region. Our study included a wide range of hospital sizes, from small hospitals having as few as 21 inpatient hospitalizations to a large medical center with 60,960 hospitalizations in 2019. One additional incoming transfer of a high-risk individual may be meaningful to a small hospital but less consequential for a large academic hospital to raise its infection control awareness for potential CRE outbreaks. Thus, transforming weighted indegree to a $\log_2$ scale made our result relevant to all hospital sizes.

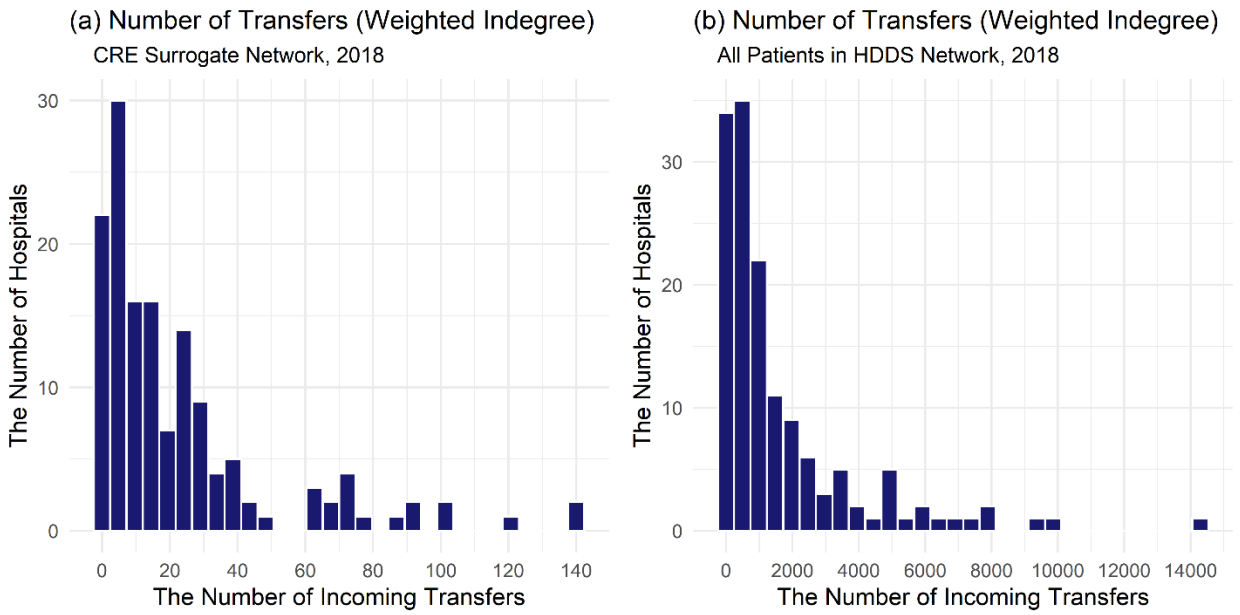


Figure 3.11 The Distribution of Weighted Indegree in CRE surrogate and All-Patient networks in 2018

The surrogate network was constructed from a small subset of high-risk patients in the HDDS. Nevertheless, the implication of the risk of increased CRE prevalence from this network should be considered by looking at the all-patient transfer volumes and capacity. Tennessee hospitals received an average of 1,666 indirect transfers (range 0–14,309) in 2018 (Figure 3.11(b)). A proportion of these patients may have a higher risk of CRE acquisitions based on their clinical and demographic characteristics. A doubling of transfers of highly susceptible patients may reflect growth in the hospital market share. However, a sudden increase in hospitalizations can occur due to a sudden increase in hospitalization volumes, like during surges in COVID-19 infections especially prior to the availability of effective treatments or vaccines. The incidence of healthcare-associated infections (HAIs) increased during the COVID-19 pandemic, and these increases corresponded to the timing of the COVID-19 surges(126–128). These hospitals are at risk of CRE outbreaks when an increase in infection prevention capacity does not accompany the increase in hospitalizations, especially when more patients require ventilators, indwelling devices, and prolonged stays in the intensive care unit. A doubling of incoming transfers of patients at risk of CRE acquisitions may be realistic during pandemic surges or outbreaks. During these situations, a small hospital that previously received 15 transfers may receive 30 transfers during these surges.

Similarly, increased occupancy in an average hospital that received around 1,000 transfers a year may not be affected by 15 additional transfers, but would if their transfers increased to 2,000.

We should also note that patients who were previously hospitalized with COVID-19 have been reported to have long-term pulmonary, cardiovascular, endocrine, and other organ system sequelae (129). The CDC reported that 20.8% US adults who survived acute COVID-19 infections experience health conditions related to their initial COVID-19 infection (130). Additionally, delay or avoidance of medical care, including urgent or emergency care and routine visits have been reported among 40% US adults during the pandemic due to COVID-19-related concerns (131). Deferred medical care may result in the worsening of the patients' chronic conditions, and complications that may deteriorate their health status. Patients with long-term COVID-19 sequelae or who experienced impact from deferred medical care may require long-term healthcare management and increased need of hospitalization in the future. Therefore, hospitals may experience an increase in the proportion of transfers of patients at-risk for CRE acquisitions, even with regular hospitalization volume. Therefore, the increase in CRE prevalence associated with the increase in high-risk patients suggested from our study results can be relevant for healthcare facilities in planning their future infection prevention measures and needed workforce capacity. The knowledge of the regional patient sharing network would inform healthcare facilities of other facilities they are connected with. Communication between healthcare facilities and coordination with public health would increase the situational awareness of current outbreaks and the risks of Multidrug Resistant Organisms (MDROs) transmissions from direct and indirect transfers.

Our networks linked hospitals through indirect transfers where a patient could spend up to 12 months in the community while still asymptomatically colonized with CRE. During admissions, the patients may not present a transfer form and were not considered by hospital staff as transfers and were not subjected to current screening protocols. Indirect transfers still pose an essential risk for CRE introduction into a hospital (1,86,132). Therefore, we urge hospitals to incorporate the history of healthcare exposures within the previous 12 months before their positive culture date and patients' underlying conditions into the decision to screen for MDROs or implement enhanced barrier precautions for hospitalized patients. Admissions screening of patients with higher risk for MDRO acquisitions can help identify the introduction of CRE or other MDROs. Additionally, contact precautions for patients at-risk of CRE acquisitions or enhanced barrier precautions for

patients with indwelling devices, especially in situations where CRE introductions or transmissions were likely.

Our study has several strengths. First, this is the first study to compare the association of hospital-level CRE prevalence with the centrality measures from hospital networks generated by different patient populations. Our study used a statistical and epidemiological approach to creating a CRE surrogate population with similar hospitalization patterns and clinical characteristics to CRE patients. The regression results showed that the surrogate network's centrality measures were most strongly associated with CRE prevalence. Furthermore, we also demonstrated the relative performance of other commonly used patient populations to assess hospital-level CRE risks.

This study was also the first study of a patient sharing network that evaluated a single measure that combined the magnitude and diversity of connection of a hospital. The statistical simulations helped us find the α value associated with CRE prevalence with the highest effect size. The α values between 0 and 1 represented a measure of connectedness that incorporates the number of hospitals (α=0) or raw indegree and the number of transfers (α=1) or commonly known as weighted indegree (121). Nevertheless, our simulations showed that the strongest association was found at α=1, or weighted indegree. In addition to having the strongest effect size, this measure provided more interpretable results for our target audience of hospitals and public health agencies. Our simulation results were fitted using Tennessee patient sharing data. Future studies can replicate our methods to validate our findings and estimate the α values for generalized indegree.

Our study results should be interpreted with some consideration. First, our study outcome was gathered from the CRE surveillance data, which may represent mostly CRE-infected patients with a more severe infection or clinical profile that require them to be hospitalized. One-time testing or diagnostic testing has limited ability to estimate actual burden of CRE colonization within a facility due to the long-term incubation and colonization period Results from a series of point-prevalence surveys where all patients in a facility underwent rectal colonization screening during non-outbreak conditions may provide a more realistic prevalence estimates of the burden of COVID-19 acquisitions and prevalent infections in a healthcare facility (82,133,134). However, such instances were resource-intensive and performed rarely. Regardless of the limitation of clinical reporting of CRE infections, TN surveillance data was a more comprehensive statewide reporting of CRE that captured CRE infections and colonization from both outpatient and inpatient

settings. We also acknowledge that our study did not include LTCFs, such as skilled nursing facilities, assisted living facilities and homes for the aged. Therefore, the study results cannot be generalized to LTCFs, which carry a significant burden of CRE (82). Future studies on CRE surrogate networks should include patient sharing data with LTCFs.

We are also aware of the potential changes in the patient transfer patterns, either resulting from changes in facility ownerships, the insurance networks, and the impact of COVID-19 pandemic. Smaller hospitals, especially in rural areas, reported a difficulty in referring patients to tertiary medical centers they previously send transfers to due to hospital inpatient and intensive care unit (ICU) bed shortages during regional COVID-19 surges. Interregional patient transfers to mitigate bed shortages have been frequently reported and resulted in the increase of the mean transfer distances between facilities, ranging from 23–352 miles for inpatients and 28–423 miles for ICU patients (135). Our preliminary analysis of the 2020 patient sharing networks from HDDS and CMS claims data showed a more interconnected network of hospitals and an increase in the number of nursing homes and smaller hospitals that received and sent transfers from larger medical centers. These connected facilities often were not previously connected through transfers in previous years of our PSN data. We are currently unable to observe whether the changes remained for the PSNs in the following years since 2020 because the discharge data were not yet available during the reporting of this study. Nevertheless, the changes and similarities of PSNs in post-pandemic era, and its impact on MDRO should be the focus of future patient sharing network research.

In conclusion, interfacility transfers of patients with similar characteristics to CRE patients, including previous healthcare exposures, indwelling devices, and underlying conditions, were associated with increasing hospital-level CRE prevalence. The changes in the characteristics of inpatient populations due to the changes in population demographics, future outbreaks, and long-term consequences of the pandemic may increase the magnitude of indirect transfers of patients at-risk for MDRO acquisitions. Indirect patient transfers may not be documented in administrative documents during hospital admission, yet they pose risk for CRE introduction and transmission in healthcare facilities. Healthcare facilities and public health can anticipate this risk by improving interfacility communications, targeted screening for MDRO acquisitions, and implementing appropriate infection control precautions.

CHAPTER IV

Third Aim: Modeling CRE Transmissions Using the Patient Sharing Network

4.1 Background

The regional prevention efforts for Multi-Drug Resistant Organisms (MDROs) have focused on interrupting transmission at healthcare facilities. Carbapenem-Resistant Enterobacterales (CRE), one of the MDROs of concern, is commonly transmitted from infectious to susceptible patients through their interactions with healthcare workers (7). The hands, clothing of healthcare workers, and equipment play a significant pathway in person-to-person transmission (136). Therefore, transmission-based precautions, including proper hand hygiene, contact precautions like universal gowns and gloves, and appropriate environmental cleaning, can successfully interrupt intrafacility transmissions of these deadly pathogens (137).

Prompt identification of MDRO threats is essential to raise facility and public awareness regarding transmission potential and to drive containment efforts. In the United States, many facilities perform colonization screening on transferred patients with a history of MDRO infection or are considered at risk of MDRO colonization (138). Nevertheless, many patients who acquired CRE without symptomatic infection receive care for other reasons (34,40). Observational studies of a regional outbreak of CRE demonstrated that these pathogens spread from one facility to another within a region through colonized patients who escape detection (86,139,140). Patients are often discharged into the community for months before re-admission to another facility and are not regarded as transfer patients. Because CRE colonization can last more than 12 months (median duration of 387 days), these patients are likely to continue to harbor CRE (42). When admitted to a facility, these patients are not presented with a transfer form and thus are not placed on contact precautions nor necessarily undergo colonization screening (40).

MDROs primarily affect vulnerable populations who are older or have underlying conditions. These patients often have more healthcare encounters and may reside in long-term care settings (11). Therefore, the community and other facilities may influence the prevalence of

MDRO within each facility. A successful containment effort in one facility should benefit the facilities that frequently receive direct transfers from the index facility. Interfacility communication is essential for successful regional containment.

When an MDRO of concern is detected at a healthcare facility, an alert to public health agencies must bring situational awareness and coordinate the containment approach (7,84,96). Some MDROs are shortlisted as targeted MDROs by the Centers for Disease Control and Prevention (CDC) in their 2019 threats report based on their recent incidence trends and consequences to human health (7). Additionally, many states, including Tennessee, made a subset of MDROs reportable diseases requiring laboratory reporting and isolate submission to their surveillance system (141). When an MDRO is detected at a healthcare facility, the alert to the jurisdictional public health agency is necessary to raise situational awareness and prompt coordination of a containment approach. CRE were listed as one of the urgent threats by the Centers for Disease Control and Prevention (CDC) in the first Antimicrobial Resistance threats report in 2013 (142) and again in 2019 (7). Due to its incidence trends and severity of health consequences. Many states, including Tennessee, made a subset of high-priority MDROs reportable to public health, requiring laboratory reporting and specimen submission to the state public health laboratory (141). CRE were listed as one of the urgent threats by the Centers for Disease Control and Prevention (CDC) in the first Antimicrobial Resistance threat report in 2013 (142) and again in 2019 (7).

In 2017, the CDC published interim guidance to contain the spread of urgent and emergent organisms. In this guidance, MDROs are classified into three response tiers based on the aggressiveness of the containment efforts recommended for their containment, with tier 1 organisms requiring the most aggressive containment response. Tier 1 organisms are the pathogens that currently have no treatment options due to their resistance to all antibiotics (pan-resistant) or have never or rarely been reported in the United States. Tier 2 organisms are typical pathogens causing healthcare-associated infections (HAI) that are not commonly identified in the region. However, they could be found more commonly in other regions in the United States. Finally, tier 3 organisms are MDROs regularly found in the region but are not endemic. CP-CRE are categorized as tier 2 or tier 3 organisms depending on their geographical endemicity and type of carbapenemase (84). In Tennessee, *Klebsiella pneumonia* Carbapenemase (KPC) CRE is

considered a tier 3 organism, while other CP-CREs are tier 2 organisms. The intervention for all tiers essentially recommended similar principles to interrupt pathogen transmission within each targeted facility, with several differences in whether more aggressive interventions are needed for organisms in tier 1 compared to tier 2 and tier 2 compared to tier 3 (84).

4.2 Rationale and Objective

Mathematical models are an essential tool for infectious disease epidemiology. They have been increasingly used to drive public health policy, project outbreak size and healthcare burden during an outbreak, direct infection control resources, and impact public health interventions on the outbreak trajectory (143). In mathematical models, a set of equations are used to describe a system's behavior, like a biological system of disease transmission. These models try to predict what happens in reality at the population level using the underlying model equations and specific values of each parameter of the equations.

One of the most common approaches to modeling disease transmission is to group individuals based on their infection status, also known as compartmental models. Two modeling approaches are often used in compartmental modeling: deterministic and stochastic approaches. One of the earliest and simplest deterministic compartmental model was proposed by Kermack and McKendrick in 1927, which divided individuals into compartments of susceptible (*S*), infected (*I*), and recovered *(R)* groups (144). This model described the introduction of a new infectious agent into a population. One or more person(s) entered the population as an infectious individual (*I)*, where all other members were susceptible to the disease. The susceptible members can acquire the disease and move into the infected group upon contact with the infectious person, with a determined probability of transmission for each contact. The conversion rate from the *S* to *I* group is also determined by the transmissibility or force of infection (β), which is a product of contact rate and the probability of transmission per contact. Infectious persons can recover or die from the disease and move into a group that is no longer susceptible to infection, or in other words, in a "removed" group, which is often referred to as the recovered group. A disease-specific recovery rate γ expresses the rate of patient transition out of the *I* group, either into the removed group or

back into the susceptible group. The flow of individuals between the disease states in a deterministic approach is determined by the sets of parameters assumed from population averages.

In reality, each individual may have a different probability of infection or recovery. Stochastic approaches reduce the discrepancy between reality and the model by enabling uncertainty in the parameters. In stochastic compartmental models, model parameters like the risk of contact, probability of developing an infection, and other parameter are randomly selected from probability distributions. Stochastic models are better at representing population variability. The role of chance in transmission events is most important when the number of infected is small, either because the total population is small or when a novel agent introduced in a population is unlikely to become endemic. On average, outbreak trajectory in stochastic model simulations match the deterministic predictions. Nevertheless, the mathematical equations of stochastic models can be very complex, and outcome estimations require more simulations to result in reliable predictions (143).

Many deterministic compartmental infectious disease models address the biological processes of various pathogens. Simulations studies using deterministic models are usually designed to answer population-level research questions and analyze the impact of practical prevention and containment strategies for infectious diseases. A relevant model for this study is the Susceptible-Infectious-Susceptible (SIS) model. In a SIS deterministic compartmental model, infectious patients do not develop meaningful immunity after recovering from infection. Instead, they return to the susceptible pool (141). Therefore, it is less focused on generating the probability of the outcome of individuals based on their clinical characteristics. In infectious disease transmissions, each person's chance of developing an infection depends on the current or past conditions of other individuals in the population and the force of infection (β). For example, the likelihood of a person developing a future infection depends on the proportion of the currently infectious population. Effective prevention could reduce the transmissibility of the disease, which is influenced by the contact rate and the probability of transmission per contact. For example, contact precautions or social distancing can reduce transmissibility by reducing the contact rate. Additionally, frequent hand washing reduces the duration that pathogens survive on a person's hand and reduce their count, thus leading to a lower probability of transmission per contact (121).

Additionally, effective therapeutic agents could shorten the disease duration, expressed in the mathematical equation as an increased recovery rate.

TDH has implemented the CDC guidance to contain MDRO transmission statewide, including CP-CRE. The spread of CP-CRE within a region is complex because it primarily spreads between patients in a healthcare facility but is also influenced by the introduction of infectious individuals via transfers from other facilities. Despite many successes in interrupting intrafacility transmissions, it is less practical to readily evaluate the impact of the containment efforts at the local or regional level because of the interconnectedness of CRE epidemiology between healthcare facilities through patient sharing. Mathematical models can predict the reduction in the regional prevalence of targeted organisms after successful prevention and containment efforts. Furthermore, they can help public health agencies set measurable goals and evaluate their current practices.

A recent study by Paul *et al.* estimated the reduction in the regional prevalence of targeted MDROs after three years of intervention if the CDC guideline was implemented at the regional level (35). This study used the patient sharing network (PSN) from the Centers for Medicare and Medicaid Services (CMS) claims data from fee-for-service beneficiaries to quantify the flow of patients between healthcare facilities from a CRE-endemic state. The CRE prevalence data from their study was sourced from the National Healthcare Safety Network (NHSN), a CDC platform for the mandatory reporting and tracking of some healthcare-associated infections by acute care and long-term care hospitals. Paul *et al.* used a deterministic compartmental model that incorporated the structure of the PSN into the risk of CRE introduction into each facility. Their study estimated that implementing the CDC guideline would reduce the targeted CP-CRE prevalence in the facility by 5-20%. Containment that reduced intrafacility transmissibility by 20% in an endemic state with an interconnected PSN was projected to reduce the regional prevalence of the targeted MDRO by 76% after three years.

We integrated the conclusions of the previous dissertation aims into this third aim by using the epidemiologic findings, CRE surveillance data, and PSN data into the mathematical model. We used the all-payer PSN of Tennessee hospitals from the second aim and the CRE surveillance data from the first and second aims. We employed the same methods and mathematical model as Paul *et al.*'s study to estimate the reduction of MDRO transmission from CDC containment

strategies in Tennessee, a state with lower CRE prevalence and dense network structure. We expected more reporting of CRE isolates from the mandatory laboratory reporting done by all facilities than from NHSN reports from inpatient hospitalizations in acute care hospitals. The results should apply to Tennessee's prevention effectiveness evaluation and be generalizable for other low-prevalence CRE states. In short, the primary objective of this study is to assess the impact of the containment strategy that incorporated the PSN and CDC guidance in Tennessee after three years using the replication of a mathematical SIS model.

4.3 Methods

4.3.1 Study Settings and Population

The setting of this study is the State of Tennessee. We included 144 hospitals who had hospitalizations in both 2018 and 2019. We grouped hospitals based on the average length of stay of the hospitalizations in 2018 and registered hospital type into 136 short-term acute care hospitals (STACHs) and 8 long-term acute care hospitals (LTACHs). Hospitals with average length of stay of >15 days were classified as LTACHs. All hospitals classified as LTACHs based on their length of stay were registered to TDH licensure as Long-Term Acute Care Hospitals (LTACHs), and vice versa. Meanwhile, the STACHs were either registered as acute care hospitals (ACHs), critical access hospitals (CAHs), or inpatient rehabilitation facilities (IRFs).

4.3.2 Infectious Disease Model

The hospital-level prevalence of CRE infections or colonizations was modeled using a mathematical model with two disease states, i.e., infectious and susceptible. The regional CRE prevalence was estimated using a multi-facility deterministic compartmental model, specifically the susceptible-infectious-susceptible (SIS) model. In this model, the occupancy of each hospital is assumed to be constant. Each infectious patient who is no longer infectious, either due to death, hospital discharge, or loss of carriage, is replaced in the facility by a susceptible patient within each hospital (Figure 4.1).

The change in CRE prevalence for each hospital over time is influenced by the number of patients currently infected, the transmissibility of CRE, the average length of hospital stays, the number of hospitalizations, and the proportion of hospitalizations transferred from other hospitals

in the network. The patient sharing network (PSN) influence on the facility-level prevalence is expressed mathematically by including the proportion of hospitalizations in each hospital transferred from other hospitals and the prevalence of CRE in these other hospitals. We assumed that CRE prevalence among patients admitted from the community was similar to CRE prevalence within each community, represented by the Health Referral Regions (HRRs) according to the Dartmouth Atlas of Healthcare (145). The prevalence and transmissibility of disease in each HRR are identical.

The change of CRE prevalence in hospital *a* (dv_a/dt) over time is governed by the following equation

$$\frac{dv_a}{dt} = \beta_a v_a(1 - v_a) - \left(\gamma + \frac{1}{\tau_a}\right) v_a + \frac{1}{\tau_a} \sum_{b=1}^{N} \frac{n_{ba}}{n_a} v_b, \ where\ b = 1, 2, \ldots N \qquad (4.1)$$

where β_a is the transmissibility of CRE from infected to susceptible patients, v_a is the current CRE prevalence in the facility, γ is the clearance rate of CRE carriage, τ_a is the average length of stay in facility a, $\frac{n_{ba}}{n_a}$ is the proportion of hospitalization at facility a that were transfers from facility b, and v_b is the prevalence of CRE in facility b. The first term on the righthand side of equation 4.1 represents the patients in each facility that newly acquired CRE through contact with existing CRE patients. The increase in new cases depends on β, the transmissibility of CRE. This study estimated β short-term and long-term acute care hospitals (STACH and LTACH, respectively) using a regression model from the statewide CRE surveillance data.

The second term on the right is a negative term representing the flow of cases out of the infected group due to clearance and end of hospitalization. Removal of infected (I) individuals depends on the disease clearance rate, γ, which was derived from the literature, and the average length of stay in the hospital, τ_a. The shorter the average hospital stay, the more considerable reduction of cases through patient discharges would be. Disease clearance rate γ represented the clearance of infectious state within each hospital, representing the clearance rate of CRE in infectious persons and the CRE-associated mortality. To maintain a balanced population in each hospital, we assumed an equal number of susceptible individuals to replace the deaths of infectious persons.

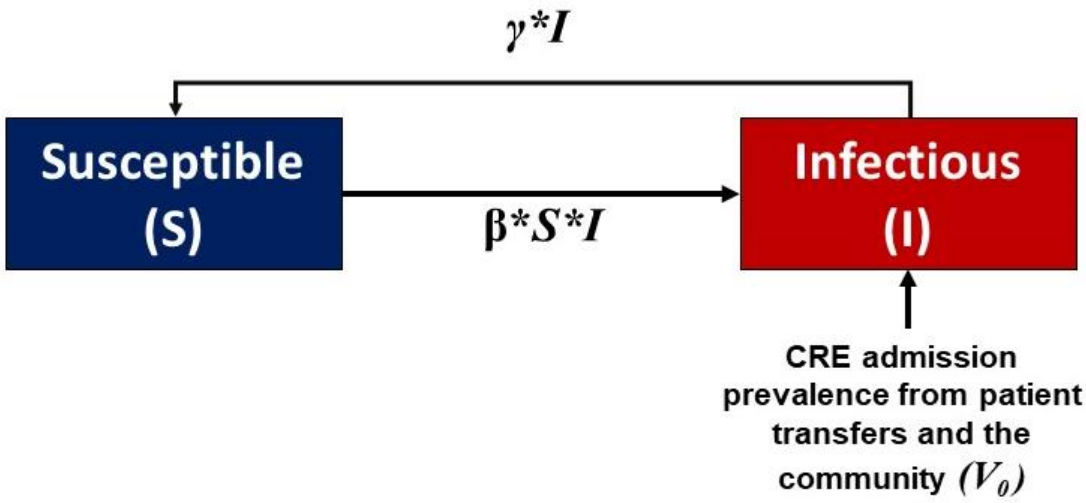


Figure 4.1 The Multi-facility SIS Model

Each facility in the PSN has an ego network, representing the network of patient flow that consists of this facility as the focal point *a* (or network term, *ego*) and all other facilities *b (*where *b=1,2,..N)* that send patients to this facility. The third term in equation 4.1 expresses the role of each facility's ego network in introducing new cases into a given hospital. The proportion of hospitalization n_a transferred from facility b (n_{ba}/n_a) and CRE prevalence in the sender facility v_b determine the number of cases introduced to the hospital *a*. The sum of each proportion of transfers from all sender facilities multiplied by their prevalence represents CRE prevalence among admitted individuals. The admission prevalence is divided by the average length of stay since more extended facility stays result in fewer new patients admitted to the facility. The summation function also means that facilities that receive transfers from more facilities or have a higher proportion of transfer patients have a greater chance of reporting CRE. Patients not transferred to another hospital are discharged to the community, represented by the eight Health Referral Regions (HRRs) in the Dartmouth Atlas of Healthcare based on the Zip Code where the hospital was located.

Several assumptions were used in the model. First, we assume CRE prevalence among admitted patients is identical for each HRR. Secondly, because CRE is overwhelmingly reported as healthcare-associated infections, we assume that transmissions occur primarily in healthcare facilities. Consequently, the community prevalence within each HRR is very low. Finally, we

assume that the transmissibility of CRE primarily depends on whether the facility was a short-term or long-term acute care hospital. Other factors, like a robust infection prevention program within each facility, may influence the intrafacility transmissibility. However, this metric is difficult to quantify and can be summarized based on hospital types. Long Term Acute Care Hospitals (LTACHs) and skilled nursing facilities have an increased risk of MDRO transmissions because they admit patients with more complex health conditions and require more extended hospitalizations.

Finally, we assume that Tennessee has a steady-state prevalence for the next three years. Paul *et al.*'s study setting is a CRE-endemic state. According to the CDC data in 2019, the proportion of CRE isolates among the hospitalized patient population in Tennessee was 3.3%, lower than several Northeastern states where CRE was endemic and Nevada and Puerto Rico, but still among the top ten states and in the United States (12). CRE was first made a reportable condition in Tennessee in 2011 for all outpatient and inpatient settings, and carbapenemase testing and isolate submission at the state public health laboratory began in July 2015. Between 2016–2021, the rate of reported prevalent CRE cases in Tennessee ranges between 10.9–11.4 cases/per 100,000 population, while the rate of CP-CRE, which is a subset of CRE cases, ranges between 3.37–3.53/per 100,000 population (Table 4.1). Tennessee reported ~700 CRE cases from all patients annually, lower than the 2,673 cases reported in New York State and 1,183 cases in Illinois in 2015 only among hospitalized patients. Based on these epidemiologic data, we can use the steady-state assumption in Tennessee to estimate the facility-level prevalence from equation 4.1.

Table 4.1 Reported CRE Cases and Rates in Tennessee Surveillance Data

Year	Tennessee Population*	All CRE		Carbapenemase-Producing CRE	
		Reported Cases	Rate/ 100,000 Population	Reported Cases	Rate/ 100,000 Population
2016	6,651,277	760	11.43	235	3.53
2017	6,778,180	796	11.21	239	3.47
2018	6,830,325	769	11.13	191	3.44
2019	6,920,119	734	10.98	203	3.4
2020	6,975,218	628	10.9	176	3.37
2021	6,975,278	693	10.9	185	3.37

*Tennessee population estimates, US Census Bureau (146)

The study used the steady-state assumption of the CRE prevalence. In a steady-state environment, the increase in cases is expected to balance the reduction of cases. Therefore, it implies that the change of prevalence over time is zero ($\frac{dv}{dt} = 0$) . Additionally, the prevalence of CRE from the patient transfers is assumed to be stable across time, expressed as v_0. Therefore, the prevalence of targeted CRE in facility v_a under a steady-state condition $v(\infty)$ can be approximated using the following equation:

$$0 = \beta\, v(\infty)(1 - v(\infty)\,) - \left(\gamma + \tfrac{1}{\tau}\right) v(\infty) + \tfrac{v_0}{\tau}$$

$$0 = \beta\, v(\infty)^2 + [\gamma + \tfrac{1}{\tau} - \beta] v(\infty) - \tfrac{v_0}{\tau}\,. \tag{4.2}$$

Using the quadratic formula, we can solve the equation above for v(∞),

$$v(\infty) = \tfrac{1}{2}\left[\left(1 - \tfrac{\gamma}{\beta} - \tfrac{1}{\beta\tau}\right) + \sqrt{\left(1 - \tfrac{\gamma}{\beta} - \tfrac{1}{\beta\tau}\right)^2 + 4\tfrac{v_0}{\beta\tau}}\right] \tag{4.3}$$

In this study, we assumed that the prevalence and transmissibility of CRE to be primarily determined by whether the hospital was a short-term or long-term stay hospital.

The following equation 4.2 approximates the steady-state prevalence in STACHs. Equation 4.2 can also be expressed as the following:

$$0 = \beta\, v(\infty)(1 - v(\infty)\,) - \left(\gamma + \tfrac{1}{\tau}\right) v(\infty) + \tfrac{v_0}{\tau}$$

Multiplying all terms by tau, we get

$$0 = \beta v(\infty)\,\tau - \beta v(\infty)^2 \tau - \tau\gamma v(\infty) - v(\infty) + v_0$$

The average length of stay in STACHs (τ) is expected to be minor, and β is a probability ranging from 0 to 1. The term $v(\infty)^2$ is also a squared product of β and τ, both small fractions and approximated to be a small value. Therefore, we can expect the term $\beta v(\infty)^2 \tau$ to be negligible. Thus, the equation with this term dropped becomes

$$0 \approx \beta v(\infty)\,\tau - \tau\gamma v(\infty) - v(\infty) + v_0$$

We then solved for $v(\infty)$ to approximate the CRE prevalence in STACHs $v_S(\infty)$ as

$$v_S(\infty) \approx \frac{v_0}{1+\gamma\beta-\beta\tau} \tag{4.4}$$

Next is the approximation of the prevalence of CRE in LTACHs. The average length of stay (τ) in LTACHs was expected to be large, while β ranges within [0,1]. Furthermore, we expected a very low CRE prevalence (v_0) among patients hospitalized from the community. Therefore, we estimated v_0 to be lower than 3.79 cases/10,000 hospitalizations for hospitals and even lower in the community. Based on these assumptions, we can expect $\frac{v_0}{\beta\tau}$ to be exceedingly small and can be dropped. Thus, we re-write equation 4.2 for long-term stay hospitals as

$$v(\infty) \approx \frac{1}{2}\left[\left(1-\frac{\gamma}{\beta}-\frac{1}{\beta\tau}\right) + \sqrt{\left(1-\frac{\gamma}{\beta}-\frac{1}{\beta\tau}\right)^2 + 0}\right]$$

which can then be translated into the following approximation for the steady-state prevalence in long-term hospitals $v_L(\infty)$:

$$v_L(\infty) \approx \left(1-\frac{\gamma}{\beta}-\frac{1}{\beta\,\tau}\right). \tag{4.5}$$

4.3.3 Model Parameters

The mathematical model parameters were sourced from either the parameters estimated in Paul *et al.*'s study or empirically from the CRE surveillance data and the Hospital Discharge Dataset (HDDS). The PSN data from the 2018 HDDS represented the flow of incoming transfers into each hospital. We used the known clearance rate of CRE acquisition from the literature (42). The transmissibility of CRE in this study was estimated using the CRE surveillance data in 2019.

4.3.3.1 Disease Parameters

Several essential disease parameters to the model were quantified from administrative and surveillance datasets, as well as from the literature. These parameters include the rate of CRE clearance or decolonization, expressed as γ, and the transmissibility of CRE in each hospital, β.

The number of deaths due to CRE infections and the clearance of CRE, either naturally or due to treatments using antimicrobial agents, cannot be quantified separately in the model. The death of a susceptible patient from non-CRE-related causes is represented in the model by replacing a susceptible person with another susceptible person. In the context of each hospital, both CRE-related deaths and clearance resulted in the replacement of an infectious person with a susceptible person. In a hospital with constant occupancy, newly admitted susceptible patients occupy all hospital beds emptied by deaths or discharges. Therefore, γ represents both CRE-related mortality and clearance rate. We set γ at 1/387 based on the median duration of CRE colonization in a population in Israel regularly tested for CRE carriage in a national containment effort (42).

Intrahospital CRE transmissibility was estimated using the calculation from the model. Current surveillance data cannot reliably estimate the β for long-term care facilities, such as nursing homes and skilled nursing facilities, due to incomplete surveillance data and HDDS data not covering these facilities. We assumed that β is only influenced by whether the hospital was an LTACH or STACH. The prevalence of CRE in each hospital can be calculated by the number of CRE positive cases *(l)* divided by the number of hospitalizations *(n)*. Therefore, the prevalence of hospitals a v_a is simply expressed as

$$v_a = \frac{l_a}{n_a} \tag{4.6}$$

Substituting the v_a in equation 4.4 with the righthand side of equation 4.5, we get an approximation of $\frac{l_a}{n_a}$ with log transformation as

$$log\,\frac{l_a}{n_a} \approx log\,\frac{v_0}{1-(\beta_a-\gamma)\,\tau_a} \quad .$$

We assume that the admission prevalence v_0 equals the prevalence within the HRRs. Thus, $v_0 \approx v_{HRR}$ With some expansion and substitution, the short-term hospital approximation is:

$$log\,\frac{l_a}{n_a} = log\,v_{HRR} + log\,\frac{1}{1-(\beta_a-\gamma)\tau_a}$$

This equation can be expanded using the Taylor series into

$$log\,\frac{l_a}{n_a} = log\,\frac{v_{HRR}}{1-(\beta_a-\gamma)\langle\tau\rangle} + (\tau_a - \langle\tau\rangle)\,\frac{(\beta_a-\gamma)}{1-(\beta_a-\gamma)\langle\tau\rangle} \tag{4.6}$$

In equation 4.6, $\langle\tau\rangle$ represents the average length of stay among STACHs. The equation above can be translated into a regression model with an intercept c_0 , two predictors $v(HRR)$ and τ, and an error term ε. The equation specifies this model:

$$log\,\frac{l}{n} = c_0 + c_v * v_{HRR} + c_\tau * \tau + \varepsilon \tag{4.7}$$

In this model c_v and c_τ are the coefficients of the predictors v_{HRR} and τ, respectively. In equation 4.7, c_τ is represented as the second term on the right.

$$C_\tau = \frac{(\beta-\gamma)}{1-(\beta-\gamma)\langle\tau\rangle}\ .$$

Using this equation, we can solve for β at short-term hospitals, β_s as

$$\beta_s \approx \gamma + \frac{c_\tau}{1+c_\tau\langle\tau\rangle}\ . \tag{4.8}$$

For LTACHs, the approximation of β can be derived from equation 4.5, with an approximation that only a fraction of all infected cases had laboratory-positive isolates, expressed as p. For long term hospitals, we first approximate the prevalence in long-term stay hospitals as:

$$\frac{l_a}{n_a} \approx p\left(1 - \frac{\gamma}{\beta}\right) - \frac{p}{\beta}.\frac{1}{\tau} \tag{4.9}$$

The equation above can be used for a regression model with one predictor $\frac{\mathbf{1}}{\boldsymbol{\tau}}$, the coefficient of the predictor as $\frac{p}{\beta}$, and an intercept of $p\left(1-\frac{\gamma}{\beta}\right)$. The coefficient $\boldsymbol{c_\tau}$ and intercept $\boldsymbol{c_0}$ of the model can be expressed as

$$c_0 = p\left(1-\frac{\gamma}{\beta}\right) \; and \; c_\tau = \frac{p}{\beta}\left(1-\frac{\gamma}{\beta}\right),$$

Which can then be translated into :

$$p = \frac{c_0}{1-\frac{\gamma}{\beta}} \; and \; p = c_\tau.\beta$$

We can then use both equations above to solve for β in long-term hospitals, β_L as

$$\beta_L = \frac{c_0}{c_\tau} + \gamma \quad \beta_L = \frac{c_0}{c_\tau} + \gamma \tag{4.10}$$

To summarize the estimation of transmissibility, we conducted two separate regressions, LTACHs and STACHs, using CRE surveillance data and the average lengths of stays from the HDDS data (i.e., γ). We did not differentiate and included both confirmed Carbapenemase-Producing CRE (CP-CRE) and non-CP-CRE in the regression models to estimate CRE transmissibility. CP-CRE were reported in fewer hospitals and would result in a regression model with less precise estimates. We gathered the coefficients and intercepts from the regressions using equations 4.7 and 4.9. These values were plugged into equations 4.8 and 4.10 to approximate the transmissibility of short-term (β_s) and long-term (β_L) stay hospitals respectively. Because transmissibility represents a probability with a [0,1] range, β_s and β_L Estimates had a log-normal distribution. The confidence interval of transmissibility values were estimated using the log-transformed mean and standard error of the coefficients of the regression models. We then exponentiated them back to a linear scale in Equations 4.8 and 4.10.

4.3.3.2 Intervention Parameters

The CDC interim guidance published in 2017 (hereafter referred to as the CDC guidance) recommends that upon detection of a targeted MDRO, the source facility should initiate healthcare investigations, contact investigations, and infection control measures. These targeted facilities include the index facility where the MDRO isolate was collected and the most likely facility(ies) to receive or send transfers to the index facility.

In the simulations, we introduced one initial CRE case in the hospital with the largest outgoing transfers (weighted-outdegree). The number of cases in each hospital in the simulation was influenced from the transmissions of current cases, imported cases from admissions from the community, and from transfers from other facilities. For each hospital in the simulations, hospital-wide containment intervention is triggered when that hospital has at least one detected CRE event after the point-prevalent screening. The intervention causes a decrease in intrafactility transmissibility after an initial delay of 30 days. The CRE event triggers containment efforts in the index hospital where CRE was detected, the upstream hospital that sends most transfers to the index hospital, and the downstream hospital that receives most transfers from the index hospital. Hospital-wide point prevalence surveys (PPS), where all current patients in each hospital were tested for CRE colonization, are conducted in each hospital 14 days after the start of the intervention. PPS are repeated every 14 days until there are no CRE-positive cases at two consecutive PPS, as suggested by the 2017 CDC guidance. Upon two PPS where no cases were detected, PPS and enhanced infection control are stopped. The intervention can be re-initiated if another CRE event is detected. CRE transmissibility in the hospital also resets to the initial values.

CDC recommends coordinating the response for MDRO containment among healthcare facilities and public health agencies. Timely reporting of targeted MDROs like Carbapenemase-Producing CRE (CP-CRE) to public health agencies such as the Tennessee Department of Health (TDH) through manual notification or electronic laboratory reporting in the surveillance data or the National Healthcare Safety Network (NHSN) is essential to allow prompt identification of a targeted MDRO and timely intervention. Public health agencies can then provide their expertise and resources for healthcare facilities to implement the appropriate infection control practices and colonization screening.

Public health should notify the most likely facility (or facilities) that sends transfers (upstream) or receive transfers (downstream) to the index facility based on the most current PSN

data. They may recommend admission screening at these facilities or colonization screening and point prevalence surveys on specific units or among high-risk patients (84). Public health investigations of targeted MDROs should also be initiated at facilities known to share patients with the index facility regularly. Public health agencies should be familiar with their regional PSN for maximal impact. Nevertheless, most local and state health departments have not described or analyzed their patient sharing network from the available administrative data sources (132).

4.3.3.3 Patient Flow Network

The flow of patients into each hospital from other hospitals was quantified by the total number of transfers n_{ba} divided by the total number of hospitalizations n_a within 12 months. The source of this information was the 2018 HDDS dataset. For this model, we used the patient transfers of all inpatients in HDDS and used an analysis using the patient transfers of CRE surrogates to represent the transfers of at-risk patients.

Patients who are colonized or infected by CRE could spend weeks to months in the community before being re-admitted to another facility and are still at risk of transmitting CRE during their hospitalizations (29,42,43,88). Patients who were not readmitted to other hospitals were considered as transfers into a specific region. These regions were grouped according to the Dartmouth Atlas of Healthcare, which assigned ZIP Codes in the United States into Health Services Areas (HSAs) and Health Referral Regions (HRRs). These regions were assigned based on the hospitalizations of people aged 65 and older covered under the fee-for-service Medicare insurance. Each HSA is a collection of ZIP codes representing the local healthcare market. The Dartmouth Atlas Project grouped ZIP codes across the United States into 3,436 HSAs where residents receive the most healthcare in hospitals.

Meanwhile, HRRs represent the regional healthcare markets for tertiary hospitals. Each HRR includes at least one hospital that performs neurosurgery and significant cardiovascular procedures and has a minimum population of 120,000 (145). The ZIP code of each hospital was cross-walked into one of eight HRRs that covered Tennessee. HRR is preferred over HSA due to its larger size and representation of the hospital patient population within the region. The number of hospitals included within each HRR reflects the regional interfacility transfers network. Additionally, a validation study of all-payer hospitalizations of people in all age groups in three

states showed that 87% (range 75–96%) of patients are hospitalized within the HRR of their residence, as opposed to 55% (14%–96%) for HSAs (147).

4.3.4 Primary Simulation

To estimate CRE transmissibility, we used Tennessee-specific data in our SIS model simulations, including the patient sharing network and CRE surveillance data. The simulations were conducted in a scenario where a new organism or outbreaks are simulated at a hospital with the largest outgoing transfers and solving equation 4.1 using the estimated β value and the prevalence of CRE in all other hospitals HRR where the hospital is located. We then quantified the number of CRE cases, which represent incidents and prevalent infections and colonizations, after three years of seeded outbreaks and intervention.

We ran one simulated outbreak using a uniform transmission parameter that used the mean value of β_s and β_L, and 34 simulated outbreaks using randomly selected transmissibility values from the distributions of β_s and β_L using their mean and standard errors. Thus, the transmissibility at differs at each simulation run. The β values were reduced starting on day 30 since the intervention started. The simulations ran on a network of Tennessee hospitals and communities connected through indirect patient transfers within 12 months.

In the simulations, the intervention is started when at least one case is detected from PPS in the hospital, assuming the notification to public health agencies occurs immediately. The intervention decreased intrafacility transmissibility beginning 30 days after the report date to allow at least two colonization screenings and the enhanced infection control measures to be established. Following CDC guidance, the intervention occurred in the index facility and facilities at risk of encountering these patients. These additional facilities include the most likely facility to transfer the infected patient and the facility to admit other infected patients discharged from the index facility. They were selected based on the facilities that send and receive most transfers from the index facility in the PSN data. The intervention stops if no patients were detected during two consecutive point prevalence surveys (35,84). Table 4.2 summarizes the data sources and parameters in the simulations.

Table 4.2 The Model Simulation Parameters and Data Sources

Model Parameters	Primary Analysis Parameters
Disease Parameters	
Transmissibility (β) for short-term hospitals (β_s) and long-term hospitals (β_L)	Regression estimates from TDH surveillance data of CRE events in 2018 and 2018 HDDS (71 hospitals, 8 HRRs) β_s = 0.039 (95% CI: 0.009, 0.119) /day β_L = 0.086 (95% CI: 0.013, 0.563) /day
Clearance rate (γ)	Literature on the median length of colonization from routinely tested population in Israel (42) γ =1/387
Intervention Parameters	
Number of cases detected in hospital to start intervention	1
Initial delay until transmissibility reduction	30 days
Negative PPS to stop intervention	2
Reduction in intrafacility transmissibility from intervention	20%
Patient flow network parameters	
The proportion of hospitalized patients that are transferred from each of the other facilities ($\frac{n_{ba}}{n_a}$)	Indirect patient transfers within 12 months from all inpatient hospitalizations in 2018 HDDS
The proportion of patients discharged to the community	The number of hospitalizations not indirectly transferred to another facility within 12 months divided by the number of total hospitalizations in 2018 HDDS
Hospital average length of stay (τ)	Length of hospital stays for each hospital in 2018 HDDS

Abbreviations: TDH, Tennessee Department of Health; HDDS, Hospital Discharge Data System; HRR, Health Referral Region; NHSN, National Healthcare Safety Network; CDC, Centers for Disease Control and Prevention; PPS, point prevalence surveys; CRE, Carbapenem-Resistant Enterobacterales

4.3.5 Measured outcome

After three years of intervention, the simulated regional prevalence of targeted CP-CRE was compared with the prevalence from an identical model with the same parameters but without reduced transmissibility. The quotient of contained prevalence divided by non-contained prevalence across multiple simulations predicted the fractional reduction in regional prevalence. We quantified the number of predicted total cases of CRE cases after three years with and without the intervention that resulted in the reduction of betas for each simulation and calculated the average fractional reduction of CRE prevalence from all 35 simulations. Additionally, we measured the number of hospitals targeted for intervention and the number of interventions performed to achieve a reduction of cases within three years.

4.3.6 Sensitivity Analyses

Sensitivity analyses were conducted to test the model under different model parameters to assess the impact of coordinated containment efforts on the regional prevalence under different circumstances, including using different transmissibility values, lower or higher reductions in transmissibility from the intervention (5% and 80%), and different network structures.

To compare the impact of the intervention in a lower prevalence state in our study with other states, we ran 35 simulation runs using the transmissibility values from Paul et al.'s study, which was derived from the National Healthcare Safety Network (NHSN) data in three states encompassing 30 Health Referral Regions (HRR) with mandatory CRE reporting among hospitalized patients. Their transmissibility estimates β_s for STACH was 0.104 (95% CI: 0.071, 0.124) per day, nearly double the β_s in the results from Tennessee data. Alternatively, the β_L for LTACHs was 0.042 (95% CI: 0.036, 0.048) per day, half of the β_L derived from Tennessee data. All other model parameters in the 35 simulations were unchanged from the primary simulation parameters.

We used a conservative reduction of intrafacility transmissibility of 20% in our primary analysis. In practice, containment efforts in each facility may result in larger or smaller reductions in transmissibility. To test the impact of different containment intensities, we ran a series of

simulations using the mean transmissibility values and other parameters in primary simulations. This time, each simulations ran using different reductions in intrafacility transmissibility due to the intervention ranging from 5% to 70%.

Finally, we ran a set of simulations using the transfer network from to estimate the impact of prioritizing facilities based on a network from CRE surrogates, a subset of the inpatient population with similar characteristics to known patients with CRE infections. The planned sensitivity analyses are listed in Table 4.3Table 4.2.

Table 4.3 Parameters of Planned Sensitivity Analyses

Sensitivity analyses parameters	Sensitivity analyses
Different disease parameters	
Transmissibility *(β)* for short-term hospitals *(β_s)* and long-term hospitals *(β_L)*	Regression estimates from Paul et al's study from NHSN in 2015 (142 hospitals, 30 HRRs) β_s = 0.104 (95% CI: 0.071, 0.124) /day β_L = 0.042 (95% CI: 0.036, 0.048) /day
Different intervention parameters	
Reduction in intrafacility transmissibility from intervention	5%–70%
Different patient sharing network	
The proportion of hospitalized patients that are transferred from each of the other facilities ($\frac{n_{ba}}{n_a}$)	Indirect patient transfers from only CRE surrogates and direct transfers of all patients in HDDS

Note: All other parameters used the primary analysis parameters in each sensitivity analysis.

4.4 Results

The network included 144 hospitals and 8 HRRs (population range: 44,487–347,532, total population 1,136,404). We quantified 244,061 interhospital transfers and 340,622 transfers from hospitals to the HRRs. Figure 4.1 shows the structure of the patient flow network.

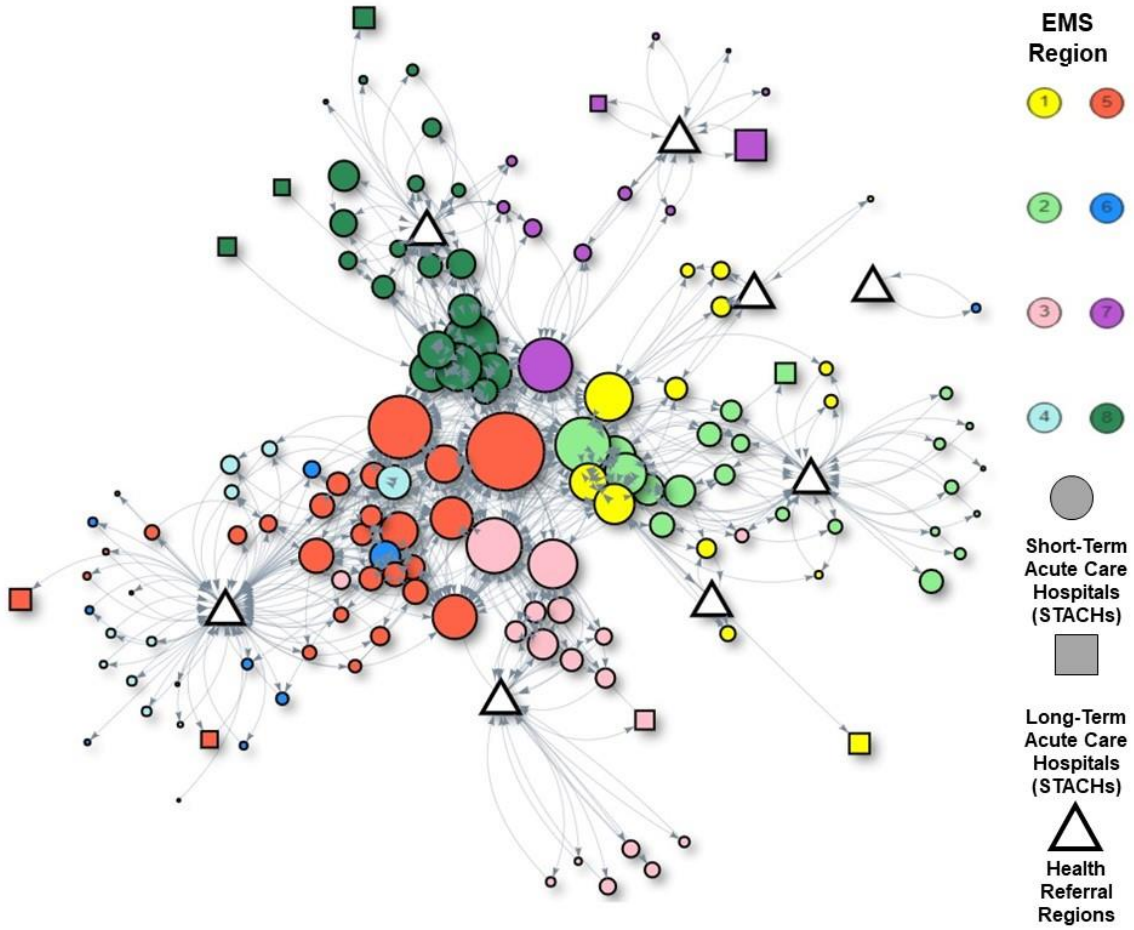


Figure 4.1 Patient flow network of hospitals in Tennessee from 2018 HDDS

Note: The patient sharing network in Tennessee was constructed from the indirect transfers of all inpatient hospitalizations in 2018 Tennessee Hospital Discharge Data within 12 months. Each colored nodes represent either a short-term (round shape) or a long-term acute care hospital (square shape). Triangles represent the Health Referral Regions. Arrows represent at least 100 transfers per year. The direction of the arrows corresponds to the direction of transfers. The size of the hospital nodes corresponds to the total patient days in 2018.

The regression models to estimate transmissibility included 646 CRE events reported from 63 STACHs and 8 LTACHs in the 2018 TDH surveillance data. Figure 4.2 shows the observed proportion of CRE events divided by the number of inpatient hospitalizations at each hospital in 2018 HDDS. Hospitals were grouped based on their average length of stay using a break at 15 days into short-term (n= 63) and long-term stay hospitals (n=8). All hospitals classified as long-term stay hospitals based on their average length of stay were registered to TDH as LTACHs. We fitted the regressions for short-term and long-term stay hospitals using equations 4.3 and 4.5. Transmissibility values were estimated by inputting the coefficients from the regression models to solve equations 4.4 and 4.6, respectively. The transmissibility for STACHs (β_s) was 0.039 (95% CI: 0.009, 0.119) per day and for LTACHs (β_L) was 0.086 (95% CI: 0.013, 0.563) /day. Equation 4.7 yields the proportion of infected or colonized patients with CRE events of 1.3%.

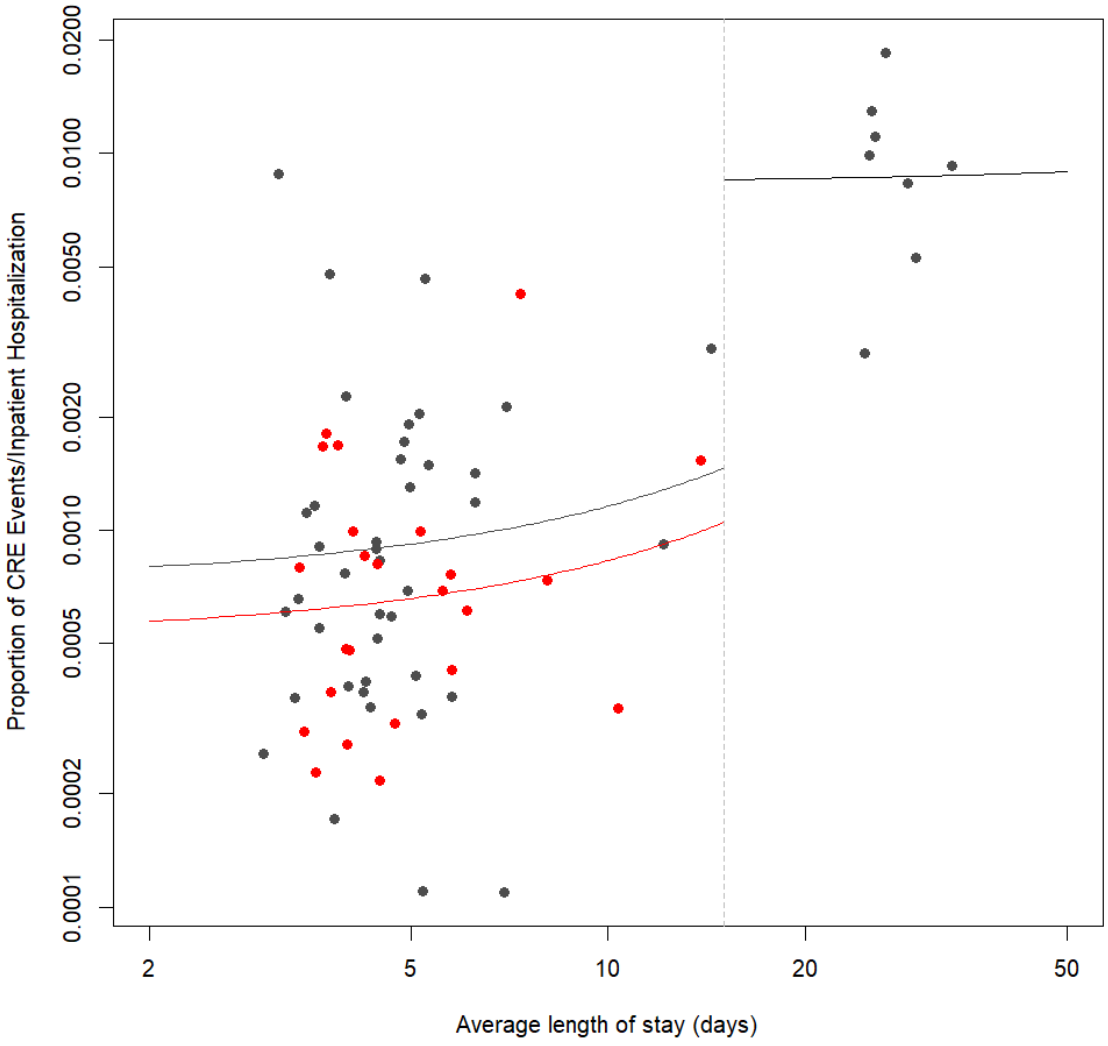


Figure 4.2 Observed proportion of CRE events per inpatient hospitalization, HDDS 2018

Note: Each dot represents a hospital in Tennessee. Dots marked in red represent hospitals in Nashville metropolitan areas. The vertical dashed line represents a natural break between the length of stay in Short-Term Acute Care Hospitals (STACHs) of $\leq$ 15 days (left of the line) and Long-Term Acute Care Hospitals LTACHs (>15 days) on the right of the dashed line. The continuous lines represent a fitted regression line used to estimate the transmissibility of CRE. The regression line and points in red represent short-term hospitals in HRR that represent Nashville metropolitan areas. The regression line in grey was fitted to all short-term or long-term stay hospitals in Tennessee, respectively. CRE events were collected from the Tennessee surveillance data, which reported all CRE positive cultures from all facilities, including hospitals.

Figure 4.3 shows the outbreak trajectory of a patient flow network with a 12-month transfer period from all inpatient hospitalizations for five years since the importation of CRE into the region. The outbreak in scenario one had fewer transmissions per day than in scenario two, which

resulted from the lower transmissibility values and fraction of hospitalizations with CRE cases estimated using the TN data. The outbreak trajectory of an intervened outbreak reached a steady-state or endemicity in the third year of the simulated outbreak, shown by the plateauing of the number of daily transmissions. The number of daily transmissions remains to slightly increase by year five to seven in the simulated outbreaks without intervention, although trending towards a steady state. An apparent reduction in the mean number of daily transmissions was shown in the mean outbreak trajectory within years three to five since the importation of the pathogens into the region.

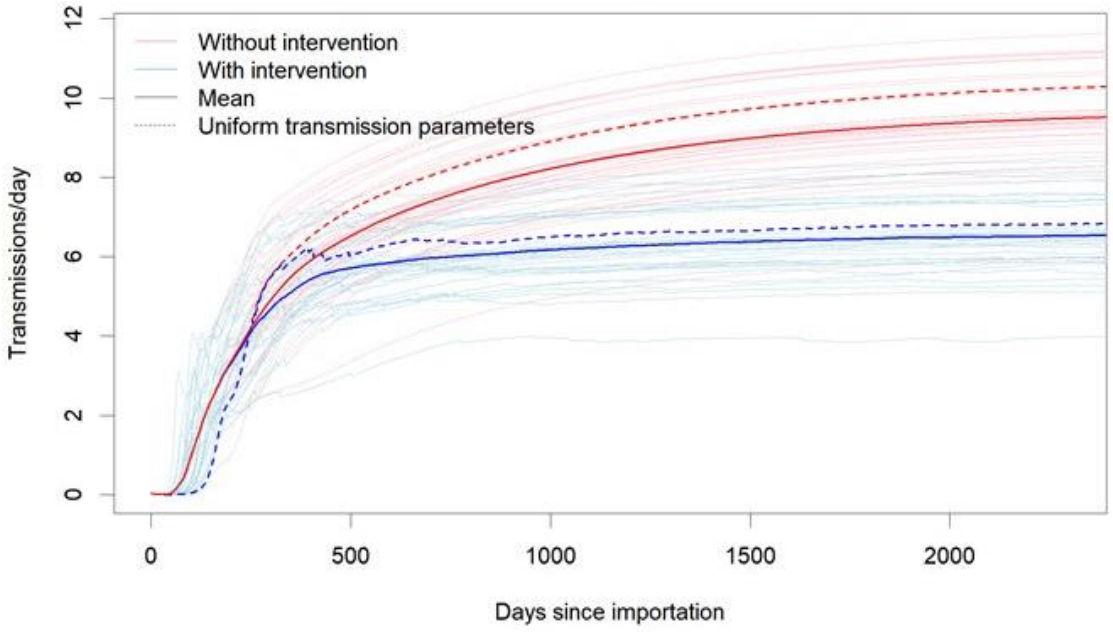


Figure 4.3 Simulated outbreak trajectories in primary simulation

Note: The figure shows Tennessee's trajectories (number of daily transmissions) of simulated outbreaks. Each pair of thin red and blue line trajectories (with and without containment) ran using randomly selected transmissibility values from a beta distribution. Each pair had different transmissibility values from other pairs of simulated outbreaks. The thick lines represent the mean outbreak trajectory of simulations with and without interventions, and the dashed lines represent the outbreak trajectory using the uniform transmission parameters from the point estimate of the regressions.

After three years of simulated outbreaks, the median reduction in the predicted number of CRE cases across 35 simulations in our primary analysis was 21% (IQR 20%–23%). This reduction required 57 interventions in 52 targeted hospitals, 36% of 144 hospitals in the network. Our sensitivity analysis using the CRE surrogates network resulted in a higher reduction of cases

of 26% (IQR 20%–38%) and required 33 interventions in 32 (24% of 144) hospitals. Furthermore, the sensitivity analysis ran using the transmissibility values in Paul *et al's* study resulted in a higher reduction of cases of 69% (IQR 68%–71%) and required interventions in all 144 hospitals. The detailed results the primary and sensitivity analyses are shown in Table 4.4.

Table 4.4 Summary of Simulation Results

Analysis type	Simulation Parameters		Simulations Outcomes		
	Transmissibility Values	**Network Data**	**Median (IQR) Reduction of CRE cases**	**Number (%) of 144 hospitals targeted for intervention**	**Number of Interventions**
Primary Analysis	TN data	All transfers within 12 months	21% (20%–23%)	52 (36%)	57
Sensitivity Analyses					
Different Network	TN data	CRE surrogates transfers within 12 months	26% (20%–38%)	32 (24%)	33
Different Transmissibility	NHSN data from three US states	All transfers within 12 months	69% (68%–71%)	144 (100%)	152

Abbreviations: TN, Tennessee; NHSN, National Healthcare Safety Network, IQR, interquartile range.
Note: All analyses pairs (with and without containment, respectively) ran using 35 simulations , including one run with the mean transmissibility parameters from the regression models and 34 runs using randomly selected transmissibility from the probability distributions using the mean and standard errors of the regression model estimates.

The result of the sensitivity analysis to assess the impact of different levels of intrafacility transmissibility reduction from 50 simulated outbreaks is shown in Figure 4.4. The fractional reduction in cases three years into the outbreak increases as the fractional reduction increases up to a plateauing of trends shown after the reduction exceeded ~60% , showing a potential benefit of having a more robust containment effort for the overall reduction in CRE prevalence.

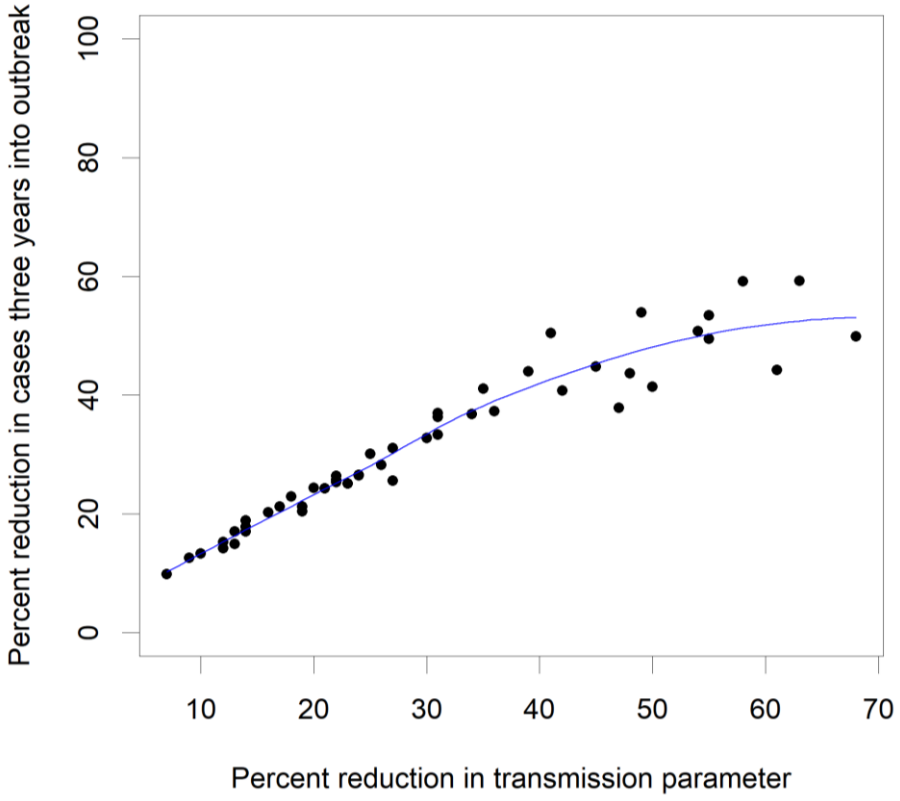


Figure 4.4 The reduction of CRE cases at different levels of transmissibility reduction

Note: Each dot represents the reduction of CRE cases after three years of outbreak simulations using the mean transmissibility values for STACHs and LTACHs at different levels of reduction in intrafacility transmission resulting from the containment effort.

4.5 Discussion

This study demonstrated the potential impact of implementing the CDC guidance for MDRO containment in a region with a dense and centralized patient sharing network like Tennessee. Our simulated outbreaks in hospitals and communities connected through all patient transfers within 12 months showed that the intervention at targeted hospitals could reduce CRE prevalence by 21% after three years. The results also showed that using the CRE surrogates network to guide the containment effort potentially reduces CRE prevalence (26%) with fewer targeted hospitals and interventions. This result affirmed the findings from the previous study aims of the potential benefit of using a patient sharing network that reflects the transfer patterns of CRE-infected or colonized patients to implement a more efficient containment strategy. Increasing the intensity of containment effort in each hospital to reduce intrafacility transmissibility further resulted in a more significant reduction in regional CRE prevalence.

Our study results resulted in a lower reduction in regional prevalence than a similar previous study by Paul *et al.* (35). The simulation in their study ran on a more heterogeneous or fragmented network structure from the direct transfer patterns of fee-for-service Medicare and Medicaid beneficiaries. In their study, the hospital-level interventions using different transmissibility and network parameters reduced CRE prevalence by 76% after interventions involving 84 (52%) of 160 hospitals in three years. In our study, the resulted prevalence reduction was 21% and required interventions in 52 (36%) 144 hospitals. The differences in our findings may be explained by the network structure used in our simulations, which connected hospitals through direct and indirect transfers within 12 months since the previous discharge dates. Our decision to use a 12-month transfer period was empirically based on the known extended CRE colonization duration of more than 12 months (42,43,45,46,49) and high re-hospitalization rates among known CRE patients (29,57,58). In contrast, Paul *et al.*'s study used a network of hospitals connected through direct transfers. However, a direct transfer network may underestimate the potential for CRE spread between facilities because patients are known to be colonized for months.

Another difference between the two studies was the higher transmissibility values for STACHs in Paul *et al.'s* study. The transmissibility values were the main driver of the time needed for a pathogen to reach a steady-state transmission level in our model. We conducted a sensitivity analysis using TN network data and Paul et al's transmissibility values, which led to a comparable

reduction in CRE cases in three years. However, the network structure influenced the number of targeted facilities required for intervention to achieve such reduction. To achieve a 69% reduction in Tennessee all 144 hospitals were targeted at least once for intervention. The network of indirect transfers in Tennessee was homogeneous, meaning most hospitals were interconnected, even with facilities covered by other HRRs. Additionally, we included patients from all payers in the transfer network, which increases our quantified hospital occupancy and transfers between hospitals.

The differences in containment impact in our study compared to previous works also implied that MDRO containment efforts in different regions may result in different levels of reduction in regional prevalence. The network structure may influence the number of hospitals targeted for intervention to achieve a similar level of prevalence reduction. Containment interventions in a dense and centralized network may require more effort from the health department infection preventionists and coordination with hospital staff and leadership. A large-scale containment effort through routine colonization screening and coordination between healthcare facilities was performed in Israel after an unprecedented outbreak of KPC-CRE after local measures failed (148). This effort required robust infrastructure and the expertise of infection preventionists and public health professionals. It resulted in a sustained reduction of MDRO transmissions and rates of other healthcare-associated infections. The containment effort also established a new infection control infrastructure at the national level.

MDRO containment efforts at the state level require coordination between public health and healthcare facilities. Additionally, it necessitates the commitment and investment of resources by healthcare facilities. The CDC guidance recommends that upon detection of a targeted MDRO, the source facility should initiate healthcare investigations, contact investigations, and enhanced infection control measures. If the index patient was not on or had a gap in their contact precautions while admitted, screening patients that overlapped in admission stay with the index patient or other patients at high risk of acquiring MDROs is recommended every 14 days after the initial detection. Screening continues until two consecutive negative rounds of screening. Enhanced infection control is also recommended for targeted facilities, including the index facility where the MDRO isolate was collected and the facility(ies) most likely to receive or send transfers to the index facility.

Conducting all elements of the bundled interventions in multiple hospitals over three years is an ambitious undertaking, even for a large, robust state Department of Health Healthcare Associated Infections (HAI) program. Nevertheless, improvements in infection control measures after on-site assessment and response (ICAR) visits can help reduce intrafacility transmissions. Virtual ICAR visits have been conducted during the COVID-19 pandemic, although the comparable effectiveness of virtual ICARs compared to in-person ICARs is yet to be evaluated. In-person ICARs could be a massive undertaking for a smaller HAI team or when the hospital or public health priorities are focused on other ongoing outbreaks such as a COVID-19 surge. The PSN can help HAI programs prioritize these visits by identifying facilities at the highest risk based on transfer patterns and possibly prioritizing in-person ICARs to high-risk facilities for CRE transmissions. These facilities may be based on their types like ventilated skilled nursing facilities (SNFs) or LTACHs or their connectivity in the network like having more connected facilities in the patient sharing network or those that have never had an in-person ICARs.

The PSN constructed from indirect transfers has helped MDRO containment in Tennessee. In January 2022, we identified a patient admitted to an index hospital with *Candida auris*, an MDRO of concern. At the time, *C. auris* had not been reported in Tennessee. TDH used a web-based interactive tool to identify downstream and upstream facilities of the index hospital based on historical transfer data, which allowed TDH epidemiologists to engage with the targeted facilities, conduct admission screenings, and inform infection control measures. Admission screening and testing of suspected cases helped identify at least 29 additional colonization cases and one clinical case in two targeted downstream facilities, including a long-term acute care hospital (LTACH) and a ventilated skilled nursing facility (vSNF). Identification of these cases triggered a containment effort in these facilities, likely preventing additional transmissions that could have occurred had the patients remained undetected. A user-friendly tool to identify downstream and upstream facilities can help public health implement the CDC guidance (91).

The study results should be interpreted with some consideration. First, mathematical models were used to estimate the transmission and prevalence of CRE using a novel strategy and assumptions regarding the epidemiology of CRE, the completeness of reporting, and the steady-state population status. Mathematical models can be parametrized with as much complexity or simplicity as the analyst's consideration. A more complex model would be more reflective of

reality but challenging to parametrize and interpret. In contrast, a simpler model requires fewer data sources and is easy to interpret. However, a simpler model generally operates under more assumptions. Further studies can be conducted on the impact of modifying intervention strategies, for example, by conducting continuous enhanced contact precautions or prioritizing facilities that are more susceptible to CRE outbreaks like LTACHs and vSNFs, or in highly-connected facilities in the region.

Secondly, our model simulations only ran on a network of Tennessee hospitals. Skilled nursing facilities (SNFs) and other LTCFs carry a considerable CRE burden. The CDC containment strategies are implemented in hospitals and LTCFs as managed by their state health departments. Starting in 2020, each licensed LTCF in TN must also have an infection preventionist in the facility to deploy the containment efforts. As more CRE case reports become available from LTCFs due to screenings and case-finding efforts, we may be able to better estimate the transmissibility values across all types of healthcare facilities in Tennessee. Simulated outbreaks using patient sharing network data that included both LTCFs and hospitals can improve our estimate of the regional impact of the containment effort.

Finally, the simulations ran using the data from 2019, before the COVID-19 pandemic. Hospital transfer patterns have changed abruptly since the pandemic began, especially during surges where hospital occupancy increases. ICU bed shortages often necessitate smaller hospitals to transfer patients to hospitals farther away than their usual referral hospitals (135,149,150). Our initial analysis of the Tennessee patient sharing network in 2020 HDDS data showed increased numbers of downstream and upstream facilities of many acute care hospitals. We also expected that the trend would continue due to the changes in hospitalization patterns from long-term sequelae of COVID-19, deferred care of many patients with chronic conditions, and future outbreaks and surges. The transmissibility of CRE may also increase due to the prolonged ICU stays and hospitalizations among patients with COVID-19 complications (126). Therefore, this analysis should be updated with newer data as they become available.

In conclusion, the MDRO containment strategies of targeted facilities connected through a patient sharing network can significantly reduce regional CRE prevalence after three years of intervention. Patient sharing network structure influences the impact of the containment impact and the number of hospitals that require containment intervention. A denser and more homogenous

network may suggest that intervention efforts require a more intensive containment effort to lower intrafacility transmissibility, which requires a more significant commitment from public health sectors and healthcare facilities.

CHAPTER V

Conclusions and Future Directions

5.1 Overview

In this dissertation, we established the relationship between hospital connectedness in a patient sharing network (PSN) with the hospital-level Carbapenem-Resistant Enterobacterales (CRE) prevalence. We also showed that this relationship was more robust for a network constructed from the transfers of CRE surrogates, a population with similar risk factors to CRE-infected patients. In the third aim, we demonstrated how the CDC guidance on Multidrug-Resistant Organisms (MDRO) containment that utilizes the PSN structure could reduce the regional CRE prevalence in three years.

The first study aim demonstrated the value of administrative and surveillance data to analyze the risk factors of re-hospitalizations within 12 months among patients with prevalent CRE infections. These risk factors were commonly collected in administrative databases and can be used to subset CRE surrogates from the general patient population. We also found that two-thirds of patients with known CRE infections were not covered by Medicare or Medicaid insurance, which suggested the importance of analyzing the patient sharing network using databases that include other payers. All-payer databases like the Healthcare Cost and Utilization Project (HCUP) or statewide hospital discharge data should be more frequently used to understand the characteristics and hospitalization patterns of patients with CRE infections and colonization.

In the second aim, we used the risk factors we identified in the first aim to generate a CRE surrogate population and analyze the patient transfer patterns from their hospitalizations. The patient-sharing network of CRE surrogates was more similar to the network generated from CRE-infected patients than all inpatient populations. Additionally, the centrality measures from the surrogate network had a stronger correlation and produced models with a better fit with CRE prevalence than the networks constructed using all inpatient populations or just Medicare and Medicaid beneficiaries. Our study was the first to evaluate the relationship between CRE prevalence and generalized in-degree. This single measure combined the magnitude and diversity of connection of a hospital using statistical simulations. The simulations showed that the number of incoming transfers, commonly known as weighted indegree, had the strongest association with

CRE prevalence and more interpretable results for our target audience of hospitals and public health agencies.

Finally, in the third study aim, we demonstrated the impact of incorporating a patient sharing network in MDRO containment efforts in Tennessee. Our simulated outbreaks showed that the intervention at targeted hospitals could still reduce CRE prevalence in a densely connected network of hospitals. Our study results strengthened previous findings on this issue and showed the comparability of the prevalence reduction from the same intervention in a different network structure. Implementing the containment strategy in a PSN constructed from transfers of all inpatients and CRE surrogates resulted in further prevalence reduction and required fewer interventions. These results further solidify the utility of the CRE surrogates network in implementing an effective containment strategy.

The overarching goal of this study is to assess the role of incorporating the patient sharing network into MDRO containment strategies. Additionally, we investigated ways to optimize the value of PSN in MDRO containment. We strengthened the arguments of using a PSN from CRE surrogates in aims 1 and 2. We also demonstrated that the selection of CRE surrogates and analysis of PSN from their hospitalizations could be performed by other health departments and researchers using commonly collected administrative data. Additionally, we demonstrated that PSN from CRE surrogates could help reduce the number of interventions and facilitate the identification of targeted facilities.

In conclusion, our study shows that incorporating PSN into a statewide MDRO containment can significantly reduce CRE prevalence, especially by using a population with a similar risk profile to patients infected with CRE.

5.2 Public Health Implications

MDRO containment at the state level requires coordination between public health and healthcare facilities to enhance infection control activities and involve floor staff and laboratory efforts to conduct patient screening. Our study shows that transfer patient sharing network structure plays a significant role in the impact of the intervention on regional CRE prevalence, even when using the same intervention and dealing with the same pathogen with similar disease parameters.

One of the most important implications of our study was the awareness that regional efforts to reduce MDRO prevalence in some areas may result in different prevalence reductions and require different levels of commitment from the regional stakeholders. Conducting the intervention in a dense, homogeneous, and centralized network may require more effort from the health department infection preventionists and coordination with hospital staff and leadership. This effort required robust infrastructure and the expertise of infection preventionists and public health professionals but has been shown to reduce MDRO transmissions and rates of other healthcare-associated infections.

The second study aim demonstrated how the study results could be relevant during and after the COVID-19 pandemic. Our study findings suggested that as the number of incoming transfers of patients with similar characteristics to CRE patients doubled, the prevalence of CRE acquisitions increased by 33% in the following year (123). A doubling of transfers of patients with risk factors of CRE acquisitions could happen during pandemic surges. A doubling of incoming transfers of patients at risk of CRE acquisitions may be realistic during pandemic surges or other future public health emergencies that significantly increase hospital admissions. These hospitals are at risk of having CRE outbreaks when an increase in infection prevention capacity does not accompany the hospitalization burden, especially when more patients require ventilators, indwelling devices, and prolonged stays in the intensive care unit.

Increased hospitalizations of high-risk patients are also relevant in non-outbreak situations in the post-COVID era. Patients previously hospitalized with COVID-19 have been reported to have long-term health consequences (129). The CDC reported that 20.8% of adults in the United States who survived acute COVID-19 infections experience health conditions related to their initial COVID-19 infection (130). Additionally, delay or avoidance of medical care may worsen the patients' chronic conditions. Patients with long-term COVID-19 sequelae or who experienced an impact from deferred medical care may require long-term healthcare management and an increased need for future hospitalizations. Therefore, hospitals may experience an increase in the proportion of transfers that were high-risk patients for CRE acquisitions, even with regular hospitalization volume.

The regional patient sharing network knowledge would inform healthcare facilities of other facilities they are connected with. Communication between healthcare facilities and coordination with public health would increase the situational awareness of current outbreaks and the risks of

MDRO transmissions from direct and indirect transfers. Our networks linked hospitals through indirect transfers where a patient could spend up to 12 months in the community while still asymptomatically colonized with CRE. During admissions, the patients may not have presented a transfer form, were not considered by hospital staff as transfers, and were not subjected to current screening protocols (1,86,132). Therefore, we urge hospitals to incorporate the history of healthcare exposures within the previous 12 months before their positive culture date and patients' underlying conditions into the decision to screen for MDROs or implement enhanced barrier precautions for hospitalized patients. Admission screening of patients with higher risk for MDRO acquisitions can help identify the introduction of CRE or other MDROs. Additionally, contact precautions for patients at-risk of CRE acquisitions or enhanced barrier precautions for patients with indwelling devices, especially in situations where CRE introductions or transmissions were likely.

5.3 Future Directions

Patient sharing networks represent a dynamic relationship between healthcare facilities and communities. Therefore, changes in its structure are inevitable, especially if we are also aware of the potential changes in the patient transfer patterns resulting from changes in facility ownership, insurance networks, and the impact of the COVID-19 pandemic. Smaller hospitals, especially in rural areas, reported difficulty referring patients to tertiary medical centers they previously sent transfers to due to hospital inpatient and intensive care unit (ICU) bed shortages during regional COVID-19 surges. These bed shortages have resulted in the changes in transfer patterns that connected facilities that were further away from each other through patient transfers. Therefore, it is necessary to analyze the changes in patient sharing network structures and their impact on MDRO transmission.

Our preliminary analysis of the 2020 PSN using hospital discharge data and Center for Medicare and Medicaid Services (CMS) claims data showed a more interconnected network of hospitals. We also observed an increase in nursing homes and smaller hospitals that received and sent transfers from larger medical centers. These facilities often were not connected through transfers in previous years of our PSN data. We are currently unable to observe whether the changes remained for the PSNs in 2021 because the discharge data were not yet available during

the reporting of this study. Nevertheless, the changes and similarities of PSNs in the post-pandemic era and their impact on MDRO should focus on future patient sharing network research.

Our study also showed encouraging results on the value of using CRE surrogates to understand interfacility MDRO transmissions better. In the second study aim, we used a case-control matching ratio from risk factors associated with re-hospitalizations among CRE-infected patients. The encouraging findings from our study on the relations between CRE surrogates PSN should be continued with validation of our methods in creating CRE surrogates, including exploring other methods to subset the surrogate populations. We should explore other methods, including creating a subset of CRE surrogates based on whether the patient met a few criteria and using a risk score threshold from a prediction model. We should also further explore the utility PSN constructed from CRE surrogate hospitalizations in identifying at-risk facilities for CRE transmissions during actual outbreaks. We will immediately include the CRE surrogate PSN into the interactive website used by TDH to identify at-risk facilities during MDRO outbreaks. This website is an interactive web tool constructed using the Rshiny application, which can be freely and securely hosted on the internet without uploading protected health information. Recent experience with the *Candida auris* outbreak has increased the engagement of TDH infection preventionists and epidemiologists in the value of utilizing PSN for their routine activities (151).

The results of the third study aim to help the Healthcare-Associated Infections and Antimicrobial Resistance (HAI-AR) program at the Tennessee Department of Health (TDH) target the anticipated level of reduction in CRE prevalence or other targeted MDROs. Because this dissertation was supported by and integrated within TDH, this study's results can help inform containment efforts and assist the evaluation of its HAI program. Additionally, the results can help them compare the impact of their containment efforts with the predicted regional prevalence. The results from the modeling study in Tennessee provided an insight into the impact of MDRO containment efforts in other regions, especially those with similar geographic and hospital network patterns as Tennessee. Our study can also contribute to the considerations of how network structure and initial regional prevalence of MDRO could influence the results of MDRO containment in diverse geographic regions.

The efforts outlined by interim guidance for MDRO containment by the Centers for Disease Control and Prevention (CDC) require an investment in public health infrastructure,

including the training and mobilization of TDH infection preventionists in containment efforts, ramping up laboratory capacity, and enhancing the surveillance system to track the results of colonization screening during facility-level interventions (84,152,153). These containment efforts can significantly reduce future MDRO prevalence in Tennessee and other regions. Additionally, the data collected from MDRO containment efforts can be used to improve the parameter estimation for future modeling studies.

Therefore, engagement and input from local and state public health agencies in epidemiologic studies are crucial to ensure that results from modeling studies are applicable and feasible, given the resources at the local and state level. Therefore, I strongly advocate for future MDRO studies involving expertise from academic institutions, national public health agencies, and state or local public health agencies.

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