Infection Control & Hospital Epidemiology (2025), **46**, 1110–1118
doi:10.1017/ice.2025.86

SHEA

Original Article

Improving containment and prevention strategies using a patient transfer network representative of patients with multidrug-resistant organisms

Rany Octaria MD, PhD, MPH[1,2,a], Stephen Deppen PhD, MS, MA[3], Allison Chan MPH[2], James C. Slaughter DrPH[4], Pamela Talley MD, MPH[5], Rachel B. Slayton PhD, MPH[6], Peter F. Rebeiro PhD, MS[7] and Marion A. Kainer MBBS, MPH[2,8,b]

[1]Vanderbilt Epidemiology Ph.D. Program, Vanderbilt University Graduate School, Nashville, TN, USA, [2]Healthcare-Associated Infections and Antimicrobial Resistance Program, Communicable and Environmental Diseases and Emergency Preparedness, Tennessee Department of Health, Nashville, TN, USA, [3]Department of Thoracic Surgery and Division of Epidemiology, Vanderbilt University Medical Center, Nashville, TN, USA, [4]Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN, USA, [5]HIV/STI/Viral Hepatitis Program, Communicable and Environmental Diseases and Emergency Preparedness, Tennessee Department of Health, Nashville, TN, USA, [6]Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA, [7]Department of Medicine, Vanderbilt University, Nashville, TN, USA and [8]Department of Health Policy, Vanderbilt University Medical Center, Nashville, TN, USA

Abstract

Objectives: Interfacility patient transfers contribute to the regional spread of multidrug-resistant organisms (MDROs). We evaluated whether transfer patterns of inpatients with similar characteristics to carbapenem-resistant Enterobacterales (CRE) case-patients (CRE surrogates) better reflect hospital-level CRE burden than traditionally used populations.

Design: We determined the risk factors for subsequent hospital admission using demographic and clinical information from Tennessee Department of Health tracked CRE case-patients from July 2015 to September 2019. Risk factors were used to identify CRE surrogates among inpatients in the 2018 Tennessee Hospital Discharge Data System (HDDS). Transfer networks of CRE surrogates, Medicare/TennCare beneficiaries, and all-inpatients with ≤365 days of intervening community stays were compared with the transfer networks of CRE case-patients in 2019. The associations between hospital-level CRE prevalence and hospitals' incoming transfer volumes from each network were assessed using negative binomial regression models.

Results: Eight risk factors for subsequent hospital admission were identified from 2,518 CRE case-patients, which were used to match CRE case-patients with HDDS inpatients, resulting in 10,069 surrogate patients. CRE surrogate network showed more structural similarities with the CRE case-patient network than with the all-inpatient and Medicare/TennCare networks. A 33% increase in hospitals' CRE prevalence in 2019 was associated with each doubling of incoming transfer of CRE surrogates in 2018 (adjusted Risk Ratio [aRR] 1.33, 95%CI: 1.1, 1.59), higher than all-inpatient (aRR 1.27, 95% CI: 1.08, 1.51) and Medicare/TennCare networks (aRR 1.21, 95% CI: 1.02, 1.44).

Conclusions: Surrogate transfer patterns were associated with hospital-level CRE prevalence, highlighting their value in MDRO containment and prevention.

(Received 2 January 2025; accepted 4 April 2025; electronically published 23 June 2025)

Introduction

Multidrug-resistant organisms (MDROs) pose a serious threat to public health by causing infections that are difficult to treat, increasing patient mortality and morbidity, and raising healthcare costs[1,2]. Some MDROs, such as carbapenem-resistant Enterobacterales (CRE), can colonize patients for months or years, allowing patients to serve as reservoirs capable of spreading these organisms during healthcare encounters[3–6]. Interfacility patient transfers between healthcare facilities pose a risk of spreading MDROs throughout a region[7–12]. Therefore, the Centers for Disease Control and Prevention (CDC) recommends using historical transfer patterns from administrative data to guide the containment and prevention of novel and targeted MDROs.[13]

The association between transfer volumes and facility-level prevalence rates has been evaluated but primarily using patient transfer networks (PTNs) described using hospitalizations of all inpatients or specific payer beneficiaries (*eg*, fee-for-service

Corresponding author: Rany Octaria; Email: ranyoctaria@gmail.com
[a]*Current affiliation*: Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA.
[b]*Current affiliation*: Infectious Diseases, Western Health, Footscray, Victoria, Australia.
Cite this article: Octaria R, Deppen S, Chan A, *et al.* Improving containment and prevention strategies using a patient transfer network representative of patients with multidrug-resistant organisms. *Infect Control Hosp Epidemiol* 2025. 46: 1110–1118, doi: 10.1017/ice.2025.86

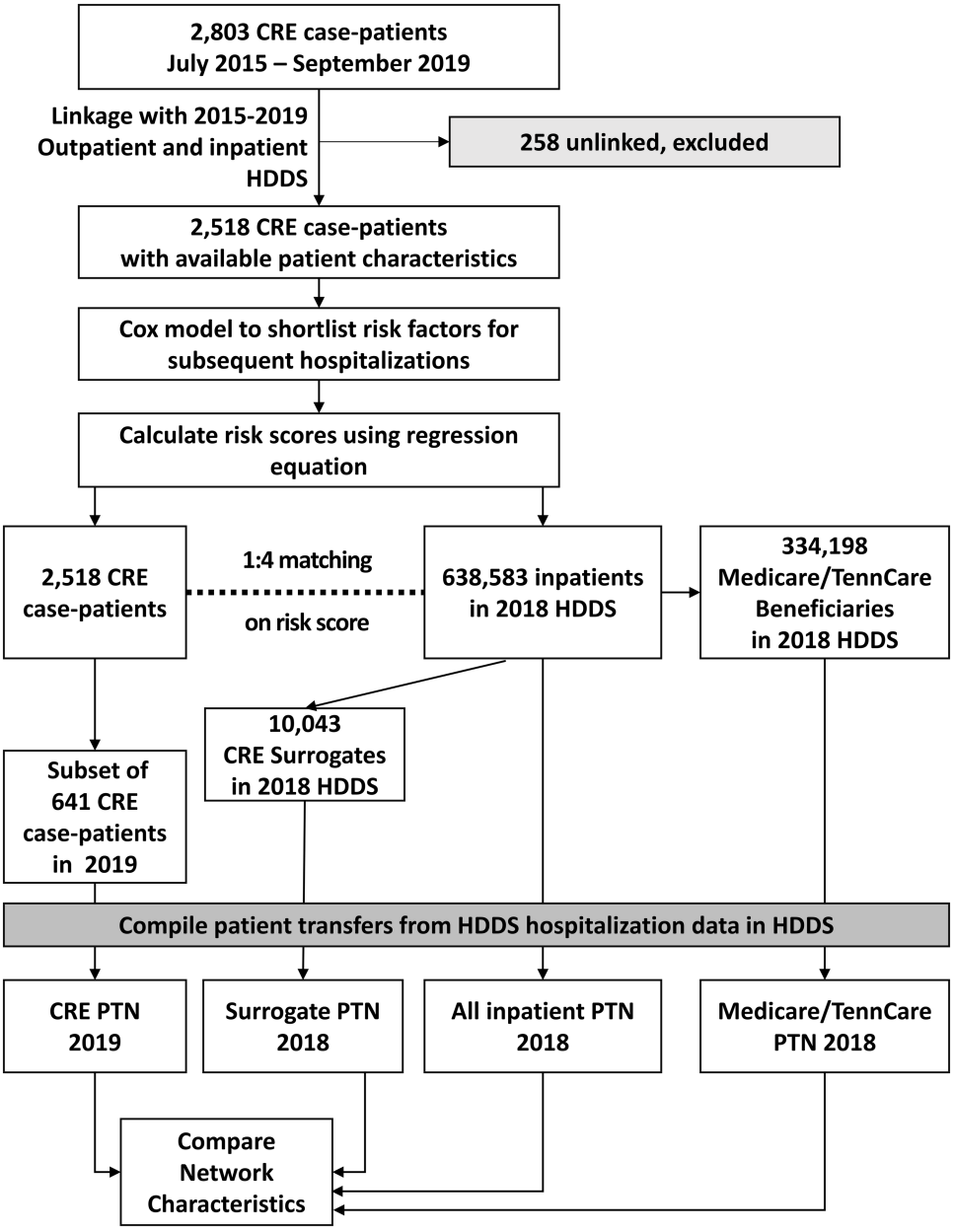

Figure 1. Study flow diagram for carbapenem-resistant Enterobacterales cases in 2015–2019 and patient transfer network constructions in Tennessee, 2018-2019. Abbreviations: CRE, Carbapenem-resistant Enterobacterales; HDDS, Hospital Discharge Data System, PTN, patient transfer network.

Medicare)[8–11], rather than PTNs derived solely from hospitalizations of persons at high risk of MDRO colonization or infection. In these studies, increased transfer volume and number of hospital connections were associated with increased MDRO cases[8]. Hospitalized patients colonized by CRE are more likely to have previous healthcare and medical device exposure, nursing home residence, and underlying medical conditions, which are more common in older patients[14–17]. Therefore, PTNs derived from hospitalization of persons with risk factors for CRE colonization or infection may be more helpful in guiding MDRO containment and prevention than PTNs from less selected groups of patients.

Using Tennessee Department of Health (TDH) CRE and hospitalization data, we evaluated whether PTNs derived from inpatients with similar characteristics to CRE case-patients would be more comparable to a PTN of CRE-colonized or infected inpatients and provide a more accurate estimate of hospital CRE burden than PTNs derived from all inpatients or Medicare/TennCare beneficiaries.

Methods

CRE surrogates

Data Source for CRE Cases. To identify the characteristics that can be used to identify CRE surrogates in the general inpatient population, we analyzed the risk factors for subsequent hospitalization among CRE case patients in Tennessee. A CRE case was defined using the 2017 Council of State and Territorial Epidemiologists case definition, which included all positive specimens within a person's life as one case[18,19]. CRE is a reportable condition in Tennessee; demographic and microbiologic data are managed using the National Disease Surveillance System Base System (NBS). The risk factor analysis included CRE

https://doi.org/10.1017/ice.2025.86 Published online by Cambridge University Press

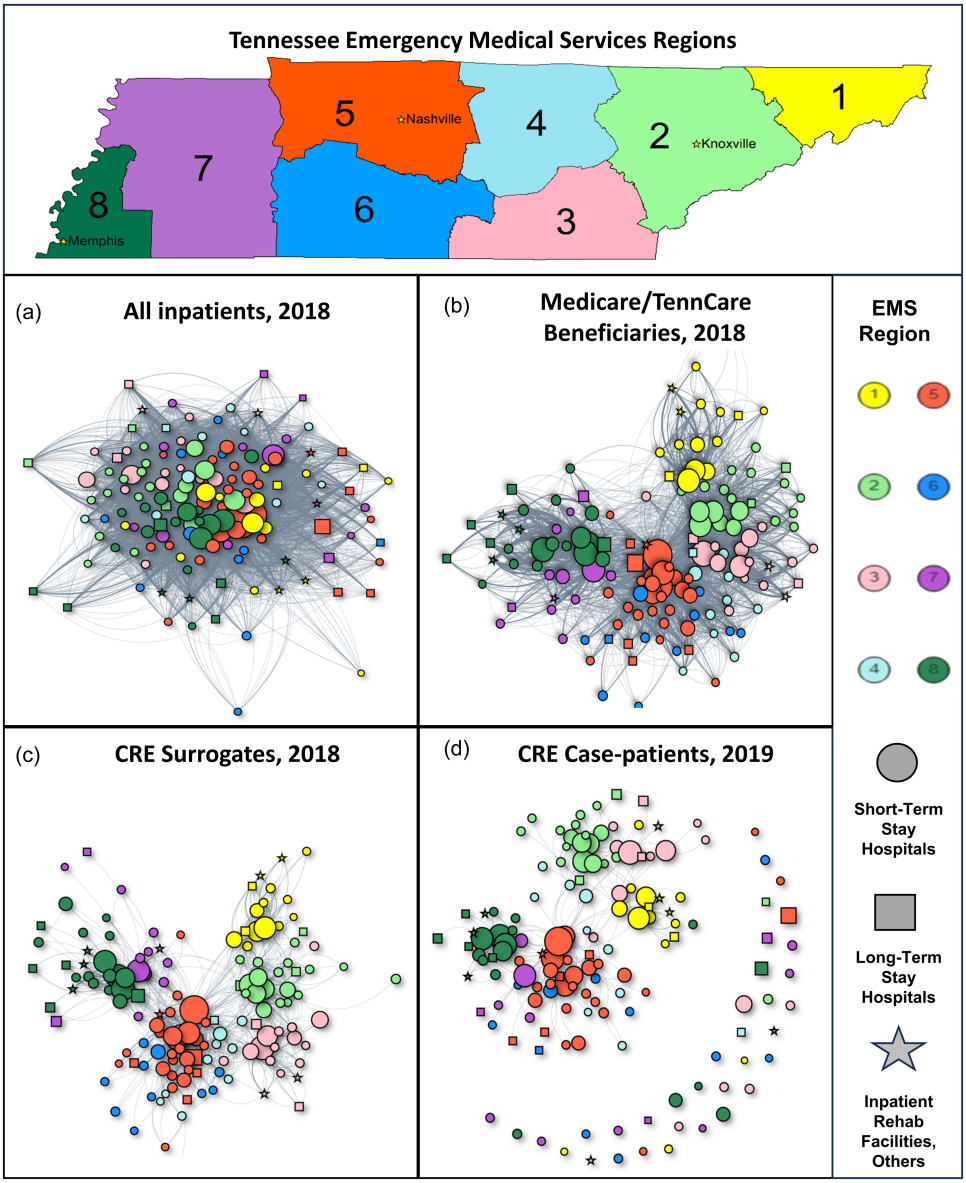

Figure 2. Tennessee emergency medical services and the structural comparison of patient transfer networks derived from different inpatient populations, 2018 and 2019. *Note*: Tennessee Hospital Discharge Data System data within 365 days, including (a) all inpatients in the 2018 Hospital Discharge Data System (HDDS), (b) Medicare/TennCare beneficiaries in the 2018 HDDS, (c) carbapenem-resistant Enterobacterales (CRE) Surrogates in the 2018 HDDS, and (d) patients with CRE infections in 2019. Each node represents one hospital, and the thickness of the connections between the nodes represents the magnitude of patient transfers. The colors of the nodes correspond to the emergency medical service regions where the hospital is located. The shape of the nodes represents the hospital type. Network diagrams were drawn using the Fruchterman-Reingold algorithm[38].

case-patients whose first CRE-positive culture collection dates were between July 1, 2015, and September 30, 2019.

Risk Factors for Subsequent Hospital Admission of CRE Case-patients. Information on healthcare exposures, underlying conditions, hospitalization details, and subsequent hospital admissions of CRE case-patients was gathered by linking patient identifiers from NBS to the Tennessee Hospital Discharge Data System (HDDS) and vital records. Patients hospitalized at their first culture-positive specimen collection date were considered inpatients, and those not hospitalized, including nursing home residents, were considered outpatients. Nursing home residence was identified using HDDS discharge status to a nursing home and by matching patient addresses to a nursing home address. Underlying conditions and healthcare exposure within 365 days before the first CRE-positive culture collection date were gathered using the International Classification of Diseases (ICD)-10 diagnostic and procedural codes, respectively.

Statistical Methods for Subsequent Hospital Admission Risk Factor Model. We used a Cox regression equation to evaluate risk factors for subsequent hospital admission among CRE case-patients within 365 days of discharge from the index hospitalization (patient's first hospitalization with a CRE-positive culture) for inpatients or since the first CRE-positive culture collection date for outpatients. We evaluated whether the model equation should be stratified by the index hospitalization status, that is, inpatient and outpatient (Details in Supplementary Materials 1).

Identification of CRE Surrogates. To identify CRE surrogates among 2018 HDDS inpatients, we used the risk factors identified in the subsequent hospital admission risk factor models. Regression model equations were used to calculate subsequent hospital admission risk scores among 2018 HDDS inpatients and included CRE case patients to match cases with potential surrogates. Case patients were matched without replacement to surrogates in a 1:4 ratio based on age in years, sex, and subsequent hospital admission

https://doi.org/10.1017/ice.2025.86 Published online by Cambridge University Press

risk scores with a caliper 0.2 of the risk score distribution standard deviation. Figure 1 shows the study flow diagram and PTN construction.

Patient transfer networks

Data Source to Construct PTNs. Patient hospitalization and transfer data were compiled using the 2018–2019 inpatient HDDS, which recorded all hospitalizations during this period in Tennessee hospitals, including short-term acute care hospitals (ACHs), long-term ACHs (LTACHs), inpatient rehabilitation facilities (IRFs), critical access hospitals (CAHs), and psychiatric hospitals. Skilled nursing facilities (SNFs) were not included in the HDDS. Transfers to out-of-state hospitals were not captured in HDDS.

Compilation and Management of Network Data. Patient transfers were characterized as (1) direct transfers or hospitalization at a different hospital within one calendar day of discharge, and (2) indirect transfers or hospitalization at a different hospital after the patient was discharged and spent 2–365 days in the community. We summarized the number of transfers between all hospital pairs. We constructed direct and total (ie, direct + indirect) PTNs from CRE case-patients in 2019 and from three patient populations in the 2018 HDDS: CRE surrogates, all inpatients, and grouped Medicare (either Medicare fee-for-services or Advantage) and TennCare beneficiaries. TennCare, Tennessee's Medicaid program, primarily serves low-income elderly individuals, those with disabilities, children, and women. Approximately 20% of TennCare beneficiaries are eligible for Medicare[20]. Transfer data from administrative datasets are typically available after the calendar year, sometimes with significant delays[21]. The CRE case-patient network was constructed from 2019 data, whereas the non-CRE inpatient networks (all-inpatients, surrogates, and Medicare/TennCare beneficiaries) were constructed from 2018 data to reflect the use of transfer data from past years to contain real-time outbreaks in public health practice.

Direct Comparisons of Network Structure. We compared whole network structures and metrics of CRE case-patients' total PTNs with total PTNs for all inpatients, Medicare/TennCare beneficiaries, and CRE surrogates to assess their suitability for estimating hospital-level CRE burden. We compared the structure and clustering in the network diagrams (Figure 2) and transfer distributions by conducting Pearson correlation tests on the transfer edgelists (ie, the number of patients transferred between each pair of sending and receiving hospitals). Additionally, we compared multiple whole-network metrics defined in Table 1 between PTNs.

Statistical Models to Assess Hospital-Level Connectedness and CRE Burden. We used multivariable negative binomial regression models with log transformation to evaluate the association between hospital connectedness metrics, generally referred to as centrality measures in network science, and hospital-level numbers of CRE events, henceforth referred to as the hospital CRE model. The primary centrality measure was weighted in degrees, representing the number of patients transferred to each hospital. Each CRE event represented a patient with a CRE-positive culture during hospitalization at that facility. Multiple positive CRE specimens obtained during the same hospitalization were considered as one event. If a patient tested positive at multiple hospitals in 2019, each hospitalization was considered an event.

The hospital CRE model evaluated the weighted in-degree using raw and transformed values to obtain a model with the best fit, defined by the lowest Akaike Information Criterion (AIC).

Table 1. Whole network measures and hospital-level centrality measures definitions

Whole Network Measures and Network Terms	Definition
Edgelist	Representation of a graph as a dataset where each row represents each connection in the network. In this context, each row includes the hospital sending the transfers, the hospital receiving the transfer, and the number of one-way transfers between the hospitals
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) 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 shortest path length between all pairs of nodes, reflecting the network's efficiency in information flow, this measure cannot be calculated if some hospitals were not connected to any other hospital in the network
Hospital-level centrality measures	Definition
Raw In-degree	The number of hospitals sending incoming transfers to each hospital
Weighted in-degree	The number of incoming transfers from any hospital
Raw Out-degree	The number of hospitals receiving transfers from each hospital
Weighted out-degree	The number of outgoing transfers from any hospital
Betweenness	The number of times each hospital serves as the shortest path to connect two other hospitals
Eigenvector	A measure of how central the hospital is relative to all other hospitals in the network

Note. The definition of network metrics is paraphrased from Jackson's Social and Economic Networks, First Edition and adapted for interfacility patient transfer network.[37]

Potential confounders were evaluated using *a priori* knowledge of the risk factors for increased CRE hospital burden (Supplementary Materials, Figure S1). The resulting model was a negative binomial with $\log_2$-weighted in-degree as the primary exposure and hospital-level numbers of CRE events as the outcome, offset by

https://doi.org/10.1017/ice.2025.86 Published online by Cambridge University Press

Table 2. Characteristics of carbapenem-resistant Enterobacterales (CRE) case-patients in 2015–2019, CRE surrogates, all inpatients, and Medicare/TennCare beneficiaries in Tennessee hospital discharge data in 2018

Patient Characteristics	CRE case-patients, July 2015- Sept 2019	CRE Surrogates, 2018	All Inpatients, 2018	Medicare/TennCare Beneficiaries, 2018
Patients (N)	2,518	10,043	638,672	334,198
Female sex (%)	1,563 (62.1)	6,234 (62.1)	369,164 (57.8)	203,015 (60.7)
Age in years (mean ± SD)	63.9 ± 18.8	63.9 ± 18.7	47 ± 27.7	63.7 ± 19.8
Race and Ethnicity (%)				
Non-Hispanic White	1,840 (73.1)	7,880 (78.5)	473,839 (74.2)	263,519 (78.9)
Non-Hispanic Black	560 (22.2)	1,710 (17.0)	105,317 (16.5)	55,109 (16.5)
Hispanic/Other	107 (4.2)	345 (3.4)	38,101 (6.0)	11,234 (3.4)
Missing	11 (0.4)	108 (1.1)	21,415 (3.4)	4,336 (1.3)
Primary insurance (%)				
Medicare/ TennCare	1,884 (74.8)	8,069 (80.3)	382,819 (59.9)	334,198 (100.0)
Commercial/Other	473 (18.8)	1,385 (13.8)	214,226 (33.5)	0 (0.0)
Uninsured	124 (4.9)	589 (5.9)	41,627 (6.5)	0 (0.0)
Missing	37 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Re-admitted within 365 da (%)	1,169 (46.4)	5,225 (52.0)	198,382 (31.1)	139,563 (41.8)
Sepsis during index hospitalization (%)	627 (24.9)	1,934 (19.3)	53,603 (8.4)	37,517 (11.2)
Healthcare exposures within 365 days before index date**				
Inpatient hospitalization(s) (%)	1,550 (61.6)	6,081 (60.5)	87,695 (13.7)	71,598 (21.4)
Total LOS at Short-term ACH, days (mean ± SD)	35.5 ± 46.9	34.5 ± 50.4	20.6 ± 92.0	22.4 ± 100.1
Previous LTACH stays (%)	133 (5.3)	66 (0.7)	610 (0.1)	684 (0.2)
Total LOS at LTACH, days (mean ± SD)	81.2 ± 50.1	46.9 ± 43.7	61.6 ±55.7	64.1 ± 54.7
Dialysis (%)	170 (6.8)	449 (4.5)	4,069 (0.6)	4,209 (1.3)
Urinary catheters (%)	241 (9.6)	401 (4.0)	2,297 (0.4)	2,565 (0.8)
Any mechanical ventilation (%)	261 (10.4)	449 (4.5)	4,197 (0.7)	3,631 (1.1)
Underlying conditions**				
Congestive heart failure (%)	855 (34.0)	3,555 (35.4)	85,025 (13.3)	73,766 (22.1)
Chronic pulmonary disease (%)	939 (37.3)	4,601 (45.8)	121,363 (19.0)	94,913 (28.4)
Renal disease (%)	882 (35.0)	3,168 (31.5)	70,625 (11.1)	63,514 (19.0)
Diabetes (%)	849 (33.7)	1,596 (15.9)	32,725 (5.1)	25,702 (7.7)
Any malignancy (%)	362 (14.4)	1,582 (15.8)	38,484 (6.0)	27,750 (8.3)
Charlson Comorbidity Index (mean ± SD)	3.9 ±3.4	3.6 ± 3.2	1.3 ± 2.0	2 ± 2.3

Abbreviations: SD, standard deviation; LOS, length of stay; Short-term ACHs, Short-Term Acute Care Hospitals; LTACHs, Long-Term Acute Care Hospitals; SNF, skilled nursing facilities.
**Healthcare exposures were quantified within the previous 365 days of the first specimen collection date for CRE case-patients infections/colonization and from the initial admission date of CRE surrogates and inpatient HDDS population.

hospital patient days. 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 centrality measures[22,23]. We then evaluated the performance of other commonly used centrality measures (defined in Table 1) instead of the weighted in-degree in the CRE hospital model, using the same log transformation and adjusted using the same confounders.

The statistical analyses were performed using R 4.0.4 (R Core Team, 2021). This study was approved with waived informed consent by the TDH Institutional Review Board[§].

Results

CRE risk factor model and CRE surrogates

There are 2,803 CRE case-patients with CRE-positive cultures were collected between July 2015 and September 2019. Of these, 45 (1.6%) were identified from positive rectal swab cultures, likely representing surveillance cultures, whereas the remaining 2,758 (98.4%) were identified from clinical cultures. Nearly 90% (n = 2,518) of CRE case-patients had at least one hospitalization during the study period and were included in the risk factor model.

https://doi.org/10.1017/ice.2025.86 Published online by Cambridge University Press

Table 3. Tennessee hospital characteristics and centrality measures of hospitals in the carbapenem-resistant Enterobacterales (CRE) surrogate total patient transfer network, 2018

Hospital Characteristics	Having >=1 CRE Event in 2019		p-value	Overall
	No	Yes		
Number of hospitals	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)	18,563 ± 2061.0	9,871 ± 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) in CRE Surrogate Total PTN, 2018				
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
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 in 2018. Categorical variables are displayed as counts (%) and continuous variables are presented as means (standard deviation).
** The Tennessee Department of Health operationally defined "high prevalence county" as two counties with increased CRE incidence during the study period.
P-values between groups were calculated using the t-test for continuous variables and the chi-square test for categorical variables.

Table 4. Whole network comparisons between transfer networks of Tennessee hospitals

Network Characteristics	All Inpatients, 2018	Medicare/ TennCare Beneficiaries, 2018	CRE Surrogates, 2018	CRE case-patients, 2019
Number of Patients	638,672	334,198	10,043	641
Number of Transfers	11,816	4,204	1,315	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	–	–
Network Diameter	3	4	5	8
ρ (95% CI) with CRE cases-patients network	0.55 (0.54, 0.56)	0.61 (0.6, 0.62)	0.60 (0.59, 0.62)	–

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 definitions of these measures are presented in Table 1.
*The correlation coefficients (ρ) and 95% confidence intervals between the edgelists from all-inpatient, Medicare/TennCare, and surrogate networks and the CRE patient network were estimated using Pearson's correlation.

Among 2,518 case-patients with at least one hospitalization during the study period, the mean age was 63.9 (SD 18.8) years, 1,564 (62.1%) were female, and 1,550 (61.6%) had ≥1 inpatient hospitalization in the previous 365 days (Table 2).

The CRE risk factor model selected eight risk factors to identify surrogates, including prior hospitalizations within 365 days before the initial positive culture, a higher Deyo-Charlson Comorbidity Index[24], a history of chronic lung disease, sepsis during the index hospitalization, having private insurance, length of stay (LOS) in LTACHs, LOS in short-term ACHs, and presence of a urinary catheter within the previous 365 days (detailed model results in Table S2). The matching process of 2,518 CRE case-patients using these risk factors resulted in 10,069 CRE surrogates from the 2018 HDDS. The surrogates had the same age and sex distributions as CRE case-patients and comparable distributions of the included risk factors. The proportion of surrogates who had subsequent hospitalization within 365 days was higher than that of CRE case-patients (52.0% vs 46.4%) (Table 2).

Patient transfer networks

The total PTN from all inpatients (n = 638,583) within the 2018 HDDS dataset included all 144 Tennessee hospitals, including 101 (70.1%) short-term ACHs, 8 (5.6%) LTACHs, 9 (8.3%) IRFs, 12 (8.3%) CAHs, and 14 (9.7%) psychiatric hospitals. Among the 731 CRE cases in 2019, 88.0% (n = 641) were hospitalized and their total transfers connected 109 (76.0%) hospitals. Seventy-three (50.7%) hospitals reported ≥1 CRE event in 2019, including all 8 LTACHs. Hospitals with CRE events were more connected to other hospitals in the network, demonstrated by having higher centrality measures, including raw and weighted in-degree and out-degree, betweenness, and eigenvector, than hospitals without CRE events (all $P < .05$) (Table 3).

The CRE surrogate total PTN connected 141 of the 144 Tennessee hospitals. The CRE surrogate network diagram and whole network metrics closely resemble the CRE PTN. The characteristics of all-inpatient and Medicare/TennCare PTNs differed from those of surrogate and CRE PTNs. The density of all-inpatient PTN was 0.57, indicating that out of all possible one-way connections between 144 hospitals (144 × 143 = 20,592), 11,737 (57%) were connected by at least one transfer. CRE and surrogate PTNs had comparably low densities. The CRE PTN had a moderate correlation with the surrogate PTN (ρ = 0.60) and Medicare/TennCare PTN (ρ = 0.61), but a lower correlation with the all-inpatient PTN (ρ = 0.55) (Table 4).

https://doi.org/10.1017/ice.2025.86 Published online by Cambridge University Press

Table 5. Comparison of prevalence rate ratios for weighted In-degree in CRE surrogates network with other networks and other centrality measures in Tennessee, 2018

Log_2-Transformed Centrality Measures	Rate Ratio (95% CI)		Multivariable Model AIC
	Crude	Adjusted	
Weighted In-Degree across Networks			
CRE Surrogates	1.14 (0.99, 1.34)	1.33 (1.13, 1.59) *	542.51
All Inpatients	1.06 (0.94, 1.21)	1.27 (1.08, 1.51) *	545.02
Medicare /TennCare Beneficiaries	1.06 (0.92, 1.23)	1.21 (1.02, 1.44) *	548.75
Other Hospital Centrality Measures in Surrogate Network			
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.
Definitions: Indegree, the number of hospitals sending incoming transfers to each hospital; weighted-in degree, the number of incoming transfers from any hospital; out-degree, the number of hospitals receiving transfers from each hospital; betweenness, the number of times each hospital serves as the shortest path to connect two other hospitals; eigenvector, a measure of how central the hospital is relative to all other hospitals in the network[1].
*Wald $P < 0.05$ of the centrality measures.
Note. All adjusted prevalence rate ratios were estimated using a multivariable model with the outcome of the number of CRE cases and adjusted for urban location, long-term acute care hospital type, and academic affiliation. The model used an offset of log 1,000 patient-days.

CRE PTN had a clustering pattern similar to that of Medicare/TennCare and surrogate PTNs. Highly connected hospitals, embedded in the center of a network diagram in the Fruchterman-Reingold layout, primarily consisted of large ACHs in Emergency Medical Services (EMS) region 5 (Nashville Metropolitan Area). Facilities in adjacent EMS regions were more connected to each other than those that were geographically farther away (Figure 2).

Hospital CRE model

The adjusted rate ratio (aRR) for the association between log_2-weighted in-degree and hospital-level CRE rate was highest for CRE surrogate PTN (aRR 1.33, 95% CI 1.13,1.59), adjusted for hospital size, type, academic affiliation, and urban location. This model also had the best fit (lowest AIC of 542.41) compared with the model with weighted in-degree from other PTNs. Among the various centrality measures in the CRE surrogate PTN, weighted in-degree had the best fit and the most robust association with CRE prevalence (Table 5).

Discussion

Our study demonstrated that the transfer patterns of the CRE surrogates better reflected the transfer pattern of CRE case-patients compared to the all-inpatient population. The number of patients transferred into each facility (weighted in-degree) had the strongest association with the number of CRE cases in the surrogate network compared with all-inpatient and Medicare/TennCare beneficiary networks, even after adjustment for facility characteristics. Understanding the transfer patterns of patients with characteristics similar to those of CRE case-patients can facilitate the identification of facilities at higher risk of CRE transmissions or importation. This information could guide public health interventions, such as prioritizing the implementation of MDRO screening in highly connected facilities.

The use of CRE surrogate network was previously demonstrated by Wolford *et al.*, who constructed networks of New York ACHs from CRE surrogates, defined as inpatients with sepsis, selected comorbidities, and prolonged hospital stays[25]. Their surrogate network was strongly correlated ($\rho = 0.81$) with hospitalized CRE cases from the National Healthcare Safety Network. Our study included outpatients and inpatients with CRE from all hospital types. The lower correlation of our CRE surrogate network ($\rho = 0.60$) compared with Wolford *et al.* may be explained by our inclusion of CRE case-patients with less severe clinical infections like urinary tract infections, which were more representative of patients contributing to regional CRE spread.

Our results suggest that a two-fold increase in incoming transfers of patients with similar characteristics to CRE case-patients was associated with a 33% increase in the hospital's CRE rates in the following year. This finding has practical implications for hospitals of various sizes. We included small hospitals with as few as 500 annual admissions and large academic hospitals with more than 50,000 admissions. To illustrate utility, an additional incoming transfer (non-transformed weighted in-degree) of a high-risk individual would be meaningful to a smaller hospital. A minor increase in the absolute number of transfers to smaller hospitals could be clinically significant and warrant improved infection prevention and control (IPC) awareness to mitigate CRE transmission. However, this additional transfer would be less sequential for large hospitals. A doubling of incoming transfers reflects a potential scenario impacting the MDRO burden for both hospital sizes.

Increases in incoming transfers of patients at a higher risk of CRE acquisition can occur due to increased transfer volumes or changes in patient population makeup. Tennessee hospitals received an average of 1,666 indirect transfers (0–14,309) in 2018. A doubling of transfers of patients at a higher risk of CRE acquisition may represent a growth in hospital market share. However, a sudden increase in hospitalizations or an increased proportion of patients highly susceptible to CRE could result from a sudden increase in hospitalization volumes, such as during surges in COVID-19, which were associated with an increased MDRO incidence[26–28]. Hospitals with increased incoming transfers could be at a higher risk of MDRO outbreaks, especially when an increase in IPC capacity does not accompany an increase in hospitalizations.

Our networks link hospitals through direct and indirect transfers with ≤365 days in the community. Hospital staff often do not consider indirectly transferred patients as transfers or include them in the facility's MDRO admission screening policy. Indirect transfers pose the risk of CRE introduction into a hospital[11,29,30]. Our findings suggest that considering a patient's healthcare exposure history to determine MDRO screening during hospital admission may be helpful. The CDC recommends interfacility communication among hospitals regarding previous MDRO cases to prevent MDRO transmissions[13]. Admission screening of patients with higher risk of MDRO acquisition may

https://doi.org/10.1017/ice.2025.86 Published online by Cambridge University Press

help facilitate more rapid and complete implementation of MDRO prevention measures.

Identification of facilities that should consider implementing MDRO screenings, including periodic prevalence surveys and admission screenings, is currently guided by PTNs constructed from all inpatients or fee-for-service Medicare beneficiaries[14,31,32]. Current recommendations prioritize influential or highly connected facilities based on historical transfer patterns for MDRO screening and enhanced infection control[14]. Our study demonstrated the added value of using a CRE surrogate network for public health agencies to identify these facilities since the transfers of surrogates are more representative of the transfer patterns of actual CRE patients and may result in more efficient, focused screening. Our previous work included the development of an interactive dashboard using all-inpatient PTN to identify potential downstream transmission when a rare MDRO was detected in an index facility[33]. This CRE surrogate network can be used similarly, especially when a concerning CRE is identified in a facility.

Our study has several strengths. We used a statistical and epidemiological approach to create a CRE surrogate population to maximize the correlation between historical transfer data and current hospital-level CRE burden. We also demonstrated the relative performance of other commonly used patient populations in assessing hospital-level CRE risks. Medicare/TennCare PTN characteristics were similar to those of CRE surrogate PTN. However, the performance of Medicare/TennCare PTN weighted in-degree was slightly inferior to that of the CRE surrogate network. Nevertheless, state and local public health can access Medicare beneficiary PTN data through a CDC-developed interactive, limited-access web application to guide preventive and containment activities[32].

Our results should be interpreted with caution. First, we mainly included CRE cases with positive clinical cultures, while CRE colonization has been documented to outweigh clinical infections at an 8:1 ratio[33]. Longitudinal colonization screening results during non-outbreak conditions may provide more realistic estimates of the facility-level CRE burden[34,35]. We did not include long-term care facilities (LTCFs), including ventilator-capable skilled nursing facilities (vSNFs), which carry a significant CRE burden[34]. Therefore, our results cannot be generalized to LTCFs and may undermine the risks of increased CRE prevalence in hospitals receiving large transfers from LTCFs. PTN structures and MDRO epidemiology may differ between states. Therefore, our findings may not be generalizable to other states and regions. Finally, transfer networks may be affected by potential changes in transfer patterns from facility ownership or insurance network changes, and the impact of the COVID-19 pandemic. Smaller hospitals, especially in rural areas, reported difficulty in referring patients to tertiary medical centers due to bed shortages during COVID-19 surges. Interregional transfers to mitigate bed shortages have been frequently reported, and the mean transfer distances between facilities have increased by 23–352 miles[36]. We should explore the impact of potential changes in PTNs on MDRO burden.

In conclusion, using a CRE surrogate PTN as proxy for CRE PTN provides a more accurate basis for implementing IPC measures than general inpatient PTN. Healthcare facilities and public health officials can prevent MDRO spread by improving interfacility communication, focused screening of patients at higher risk for MDROs, and implementing appropriate IPC.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/ice.2025.86

Acknowledgements. We thank the Vanderbilt University Epidemiology PhD Program for supporting this project, and the Tennessee Department for surveillance data collection, management, and support. The authors thank the following individuals for their contributions: Prabasaj Paul, Hannah Wolford, Matthew Estes, Kristina McClanahan, and Carolyn Stover.

Author contributions. RO, AC, and MAK contributed to the design and implementation of the research, while RO, AK, RBS, PT, SD, JCS, and PFR contributed to the analysis of the results and the writing of the manuscript. MAK and PT conceived the original and supervised the project.

Financial support. The Tennessee CDC Emerging Infections Program and Vanderbilt University supported this study (Grant # 5 NU50CK000491-03-00).

Competing interests. All authors have completed the International Committee of Medical Journal Editors to disclose potential conflicts of interest. Dr. Kainer reports grants and non-financial support from the Centers for Disease Control and Prevention during the conduct of the study; personal fees and non-financial support from the Infectious Disease Consulting Corporation, personal fees and non-financial support from Pfizer, and personal fees from Gilead outside the submitted work; Dr. Rebeiro reports personal fees from Gilead, personal fees from Johnson & Johnson, and grants from NIH/NIAID outside the submitted work.

Disclaimer. The findings and conclusions of this study are those of the authors and do not necessarily represent the official position of the Tennessee Department of Health or the Centers for Disease Control and Prevention.

References

1. Centers for Disease Control and Prevention. *2022 Special Report: COVID-19 U.S. Impact on Antimicrobial Resistance*.; 2022. Accessed July 14, 2022. https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf
2. Johnston KJ, Thorpe KE, Jacob JT, Murphy DJ. The incremental cost of infections associated with multidrug-resistant organisms in the inpatient hospital setting—A national estimate. *Health Serv Res* 2019;54:782–792. doi: 10.1111/1475-6773.13135
3. Zimmerman FS, Assous MV, Bdolah-Abram T, Lachish T, Yinnon AM, Wiener-Well Y. Duration of carriage of carbapenem-resistant Enterobacteriaceae following hospital discharge. *Am J Infect Control* 2013;41:190–194. doi: 10.1016/j.ajic.2012.09.020
4. Haverkate MR, Weiner S, Lolans K, *et al.* Duration of colonization with Klebsiella pneumoniae carbapenemase-producing bacteria at long-term acute care hospitals in Chicago, Illinois. *Open Forum Infect Dis* 2016;3: ofw178. doi: 10.1093/ofid/ofw178
5. Bar-Yoseph H, Hussein K, Braun E, Paul M. Natural history and decolonization strategies for ESBL/carbapenem-resistant Enterobacteriaceae carriage: systematic review and meta-analysis. *J Antimicrob Chemother* 2016;71:2729–2739. doi: 10.1093/jac/dkw221
6. Mo Y, Hernandez-Koutoucheva A, Musicha P, *et al.* Duration of carbapenemase-producing enterobacteriaceae carriage in hospital patients. *Emerg Infect Dis* 2020;26:2182–2185. doi: 10.3201/eid2609.190592
7. Barnes SL, Harris AD, Golden BL, Wasil EA, Furuno JP. Contribution of interfacility patient movement to overall methicillin-resistant Staphylococcus aureus prevalence levels. *Infect Control Hosp Epidemiol* 2011;32:1073–1078. doi: 10.1086/662375
8. Donker T, Wallinga J, Slack R, Grundmann H. Hospital networks and the dispersal of hospital-acquired pathogens by patient transfer. *PloS One* 2012;7. doi: 10.1371/journal.pone.0035002
9. Ray MJ, Lin MY, Weinstein RA, Trick WE. Spread of carbapenem-resistant Enterobacteriaceae among Illinois healthcare facilities: the role of patient sharing. *Clin Infect Dis* 2016;63:889–893. doi: 10.1093/cid/ciw461
10. Nekkab N, Crépey P, Astagneau P, Opatowski L, Temime L. Assessing the role of interfacility patient transfer in the spread of carbapenemase-producing Enterobacteriaceae: the case of France between 2012 and 2015. *Sci Rep* 2020;10:14940. doi: 10.1038/s41598-020-71212-6

11. Bower CW, Fridkin DW, Wolford HM, *et al.* Evaluating movement of patients with carbapenem-resistant Enterobacteriaceae infections in the Greater Atlanta Metropolitan area using social network analysis. *Clin Infect Dis* 2020;70:75–81. doi: 10.1093/cid/ciz154
12. Lapp Z, Octaria R, O'Malley SM, *et al.* Distinct origins and transmission pathways of blaKPC Enterobacterales across Three U.S. states. *J Clin Microbiol* 2023;61:e00259–23. doi: 10.1128/jcm.00259-23
13. Centers for Disease Control and Prevention. Public Health Strategies to Prevent the Spread of Novel and Targeted Multidrug-resistant Organisms (MDROs). Published online 2023. https://www.cdc.gov/hai/mdro-guides/index.html
14. Bhargava A, Hayakawa K, Silverman E, *et al.* Risk factors for colonization due to carbapenem-resistant Enterobacteriaceae among patients: exposed to long-term acute care and acute care facilities. *Infect Control Hosp Epidemiol* 2014;35:398–405. doi: 10.1086/675614
15. Guh AY, Bulens SN, Mu Y, *et al.* Epidemiology of carbapenem-resistant enterobacteriaceae in 7 US communities, 2012-2013. *JAMA - J Am Med Assoc* 2015;314:1479–1487. doi: 10.1001/jama.2015.12480
16. Van Loon K, Voor In'T Holt AF, Vos MC. A systematic review and meta-analyses of the clinical epidemiology of carbapenem-resistant enterobacteriaceae. *Antimicrob Agents Chemother* 2017;62(1):e01730–17. doi: 10.1128/AAC.01730-17
17. Kassem A, Raed A, Michael T, *et al.* Risk factors and outcomes of patients colonized with carbapenemase-producing and non-carbapenemase-producing carbapenem-resistant Enterobacteriaceae. *Infect Control Hosp Epidemiol* 2020;41:1154–1161. doi: 10.1017/ice.2020.266
18. Council of State and Territorial Epidemiologists. Change in Case Definition from Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae (CP-CRE) to Carbapenemase-Producing Organisms (CPO), 2017. https://cdn.ymaws.com/www.cste.org/resource/resmgr/ps/ps2022/22-ID-04_CPO.pdf
19. Council of State and Territorial Epidemiologists. Standardized Definition for Carbapenem-Resistant Enterobacteriaceae (CRE) and Recommendation for Sub-Classification and Stratified Reporting.; 2015. Accessed June 9, 2021. https://cdn.ymaws.com/www.cste.org/resource/resmgr/2015PS/2015PSFinal/15-ID-05.pdf
20. Division of TennCare. Aged, Blind and Disabled Manual: Qualified Medicare Beneficiary. Published online March 8, 2024. https://www.tn.gov/content/dam/tn/tenncare/documents/QualifiedMedicareBeneficiary.pdf
21. Strengths and Limitations of CMS Administrative Data in Research | ResDAC. Accessed November 27, 2024. https://resdac.org/articles/strengths-and-limitations-cms-administrative-data-research
22. Feng C, Wang H, Lu N, *et al.* Log-transformation and its implications for data analysis. *Shanghai Arch Psychiatry* 2014;26:105. doi: 10.3969/J.ISSN.1002-0829.2014.02.009
23. Interpreting Log Transformations in a Linear Model | University of Virginia Library Research Data Services + Sciences. Accessed May 13, 2022. https://data.library.virginia.edu/interpreting-log-transformations-in-a-linear-model/
24. Ladha KS, Zhao K, Quraishi SA, *et al.* The Deyo-Charlson and Elixhauser-van Walraven comorbidity indices as predictors of mortality in critically ill patients. *BMJ Open* 2015;5:8990. doi: 10.1136/BMJOPEN-2015-008990
25. Wolford H, O'Hagan J, Paul P, *et al.* Comparing inter-hospital patient movement patterns to better understand mechanisms for regional dissemination of carbapenem-resistant Enterobacteriaceae. *Open Forum Infect Dis* 2019;6:S859. doi: 10.1093/OFID/OFZ360.2159
26. Weiner-Lastinger LM, Pattabiraman V, Konnor RY, *et al.* The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections in 2020: a summary of data reported to the National Healthcare Safety Network. *Infect Control Hosp Epidemiol* 2022;43:12–25. doi: 10.1017/ICE.2021.362
27. Cybersecurity & Infrastructure Security Agency. Healthcare and Public Health Sector. Accessed May 26, 2022. https://www.cisa.gov/healthcare-and-public-health-sector
28. French G, Hulse M, Nguyen D, *et al.* Impact of hospital strain on excess deaths during the COVID-19 pandemic — United States, July 2020–July 2021. *MMWR Morb Mortal Wkly Rep 2021*;70:1613–1616. doi: 10.15585/MMWR.MM7046A5
29. Ray MJ, Lin MY, Tang AS, *et al.* Regional spread of an outbreak of carbapenem-resistant enterobacteriaceae through an ego network of healthcare facilities. *Clin Infect Dis* 2018;67:407–410. doi: 10.1093/cid/ciy084
30. Slayton RB, Toth D, Lee BY, *et al.* Vital signs: Estimated effects of a coordinated approach for action to reduce antibiotic-resistant infections in health care facilities - United States. *Am J Transplant* 2015;15:3002–3007. doi: 10.1111/ajt.13555
31. Cincotta SE, Walters MS, Ham DC, et al. Regional impact of multidrug-resistant organism prevention bundles implemented by facility type: A modeling study. *Infect Control Hosp Epidemiol*. 2024;45(7):856–863. doi: 10.1017/ice.2023.278
32. Octaria R, Cincotta S, Healy J, *et al.* An interactive patient transfer network and model visualization tool for multidrug-resistant organism prevention strategies. *Antimicrob Steward Healthc Epidemiol ASHE* 2023;3:s120–s122. doi: 10.1017/ash.2023.403
33. Lee BY, Bartsch SM, Wong KF, *et al.* Tracking the spread of carbapenem-resistant Enterobacteriaceae (CRE) through clinical cultures alone underestimates the spread of CRE even more than anticipated. *Infect Control Hosp Epidemiol* 2019;40:731–734. doi: 10.1017/ice.2019.61
34. Mckinnell JA, Singh RD, Miller LG, *et al.* The SHIELD orange county project: multidrug-resistant organism prevalence in 21 nursing homes and long-term acute care facilities in Southern California. *Clin Infect Dis* 2019;69:1566–1573. doi: 10.1093/cid/ciz119
35. Centers for Disease Control and Prevention (CDC). Guidance for control of infections with carbapenem-resistant or carbapenemase-producing Enterobacteriaceae in acute care facilities. *MMWR Morb Mortal Wkly Rep* 2009;58:256–260.
36. Michelson KA, Rees CA, Sarathy J, *et al.* Interregional transfers for pandemic surges. *Clin Infect Dis* 2021;73:e4103–e4110. doi: 10.1093/CID/CIAA1549
37. Jackson MO. *Social and Economic Networks*. Princeton University Press; 2008.
38. Hansen DL, Shneiderman B, Smith MA, Himelboim I. Installation, orientation, and layout. *Anal Soc Media Netw NodeXL Insights Connect World*. Published online January 1, 2019:55-66. doi: 10.1016/B978-0-12-817756-3.00004-2

https://doi.org/10.1017/ice.2025.86 Published online by Cambridge University Press