HOSPITAL LEVEL CHARACTERISTICS ASSOCIATED WITH CLOSTRIDIUM DIFFICILE RATES AND OUTCOMES

A thesis

submitted by

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In partial fulfillment of the requirements
for the degree of

Master of Science

in

Clinical and Translational Science

TUFTS UNIVERSITY

Sackler School of Graduate Biomedical Sciences

May, 2015

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ABSTRACT

The incidence of *Clostridium difficile* infection (CDI) has increased steadily during the past fifteen years. Previous studies have shown that CDI rates and outcomes vary among hospitals with different characteristics though none of these studies adjusted for the patient case mix.

We used data from the Nationwide Inpatient Sample (NIS), which is part of the Healthcare Cost and Utilization Project (HCUP), from the years 2003 to 2012 for this cross sectional study. We compared the odds of a CDI diagnosis and secondary outcomes of CDI, including in-hospital case fatality, duration of hospitalization, and total hospital charges, according to different hospital characteristics - which included location, teaching status, size, multi-hospital membership status, and number of ancillary staff. All statistical models were adjusted for patient characteristics, including age, sex, the expected primary payer, socioeconomic status, and comorbidities.

Our study population consisted of 58% females with an average age of 47.9 (SD ± 27.9) years. There were 644,765 patients with a CDI diagnosis, of which 450,257 were considered to have secondary CDI. Patients who were admitted to urban as compared with rural hospitals had an increased odds of having a CDI diagnosis (adjusted OR 1.53, 95% CI 1.45, 1.61), increased odds of in-hospital death with CDI (adjusted OR 1.36, 95% CI 1.29, 1.42), a longer duration of hospitalization for patients with CDI by 46% (95% CI 43%, 49%) and an increase in total charges for patients with CDI by 84% (95% CI 75%,

93%). Teaching hospitals when compared with nonteaching hospitals were also associated with an increased odds of CDI (adjusted OR 1.21, 95% CI 1.16, 1.26), in-hospital death with CDI (adjusted OR 1.12, 95% CI 1.08, 1.16), increase in duration of hospitalization for CDI by 12% (95% CI 10%, 13%) and an increase in total hospitalization charges for CDI by 9% (95% CI 7%, 11%). The Northeast had significantly higher rates of CDI, CDI case fatality, duration of hospitalization for CDI, and amount of total charges when compared to other regions of the country. Multi-hospital membership status was found to be significantly associated with the duration of hospitalization. We also found significant associations between CDI rates and outcomes with several nursing categories.

There was significant variation in CDI rates and outcomes for hospitals based on location, teaching status, region, and hospital classification, even after adjusting for patient-level characteristics.

ACKNOWLEDGMENTS

I could not accomplish the work in this thesis without the help and support of many people whom I would like to thank: Matthew Finkelman, for guiding me through the data analysis and for his invaluable statistical advice; John Wong, who offered great insight to the study design and gave excellent recommendations to the order of my manuscript; Jennifer Chow for her SAS and clinical expertise; and Laura Kogelman, who was always ready to help with all my fellowship clinical duties so that I may have time to dedicate to this thesis.

I owe special gratitude to my two main mentors. I want to give thanks to Shira Doron for the countless hours she has spent with me on this and other projects. I admire the never-ending enthusiasm, respect, and patience with which she has always shown me. I also want to give special thanks to David R. Snydman for being my role model. He embodies all that I want to be as a researcher and physician in infectious diseases. He has given me great support and has instilled confidence in me for the next stage of my career.

I want to thank all of my fellow Sackler students and professors as they have made the M.S. a rewarding, fun experience.

I also thank my parents, Edgar and Veronica Sanchez, for their guidance throughout the years, and helping me strive to always do better. I want to thank my sisters, Elaine and Eliza, for helping read and critique all of my manuscripts and always calling me out on my mistakes.

Of course, I especially want to thank my wife, Alda, for always being by my side. I could not have undergone the rigors of residency, and now fellowship, without her unwavering support, patience, and love. Now we can relax, enjoy our time off, and look forward to warmer days!

This thesis was supported by National Institutes of Health Grant # 5T32 AI055412-09, "Clinical Research Training in Infectious Disease."

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ABBREVIATIONS USED

CBSA: Core Based Statistical Area

CDI: Clostridium Difficile Infection

CI: Confidence Interval

CNA: Certified Nursing Aide

FTE: Full Time Equivalent

HCUP: Healthcare Cost and Utilization Project

HIV/AIDS: Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome

ICD-9-CM: International Classification of Diseases, Clinical Modification, 9th Revision

LPN: Licensed Practical Nurse

NEC: Not Elsewhere Classified

NIS: Nationwide Inpatient Sample

NOS: Not Otherwise Specified

RN: Registered Nurse

SD: Standard Deviation

INTRODUCTION

Clostridium difficile infection (CDI) is associated with substantial morbidity and case fatality. Disruption of the normal gut flora, especially by antibiotics, allows *C. difficile* to proliferate and cause a wide spectrum of disease, from diarrhea to life-threatening colitis. Between 2001 and 2010, the incidence of CDI in U.S. hospitals increased from 45 cases to 82 cases per 10,000 patients.[1] CDI is now linked to 14,000 deaths per year with annual costs in excess of one billion dollars. In a 2013 report, the Centers for Disease Control and Prevention designated CDI as one of three pathogens with its highest threat level and recommended immediate and aggressive action.[2]

Despite increasing rates of community acquired CDI, the majority of cases remain associated with health care facilities. Among hospitals in California, Arizona, and Minnesota, those in urban locations and offering transplant services had the highest rates.[3] Without adjusting for patient comorbidities, the Northeast had the highest rates of CDI, and the Midwest had the highest CDI case fatality.[1,3,4] Part of this may be attributable to spread of a new, more virulent strain, identified as BI/NAP1/027, discovered in 2002, and first observed in the Northeast in Pittsburgh, Pennsylvania, and Quebec, Canada..[5,6] In 2013, using reported CDI rates in the National Health and Safety Network, the Centers for Disease Control and Prevention identified CDI test type, facility bed size, medical school affiliation, and admission prevalence of CDI as covariates to risk-adjust baseline CDI rate for a particular hospital.[7] However, because patient characteristics have been shown to influence CDI rates and outcomes, ideally, a

predictive model would also adjust for the hospital case mix.[8-10] The relationship between hospital characteristics and CDI incidence, case fatality, and duration of hospitalization remains unknown.

The primary objective of this study then was to determine hospital-level risk factors that are associated with the occurrence of CDI after adjusting for differences in the patient population. Secondary study objectives included determining the association of these hospital-level risk factors with CDI outcomes, including in-hospital case fatality, duration of hospitalization, and hospitalization charges among patients with diagnosed CDI after adjusting for characteristics of the patient population.

MATERIALS AND METHODS

Data source:

All data were extracted from the 2003 to 2012 Nationwide Inpatient Sample (NIS) database, the largest all-payer database in the United States containing up to 8 million annual inpatient discharges from approximately 1,000 hospitals. Maintained as part of the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality, it consists of a 20% sample of discharges from all participating nonfederal acute care hospitals. The patients included in this database have a primary discharge diagnosis and up to 24 secondary diagnoses listed.[11] Each year of the NIS contains core data elements that include patient characteristics, hospital file data elements (hospital characteristics), and severity file data elements (comorbidities). Of note, beginning in 2012, the NIS was redesigned to sample all discharges from every hospital. Previously, the NIS sampled discharges only from a subset of hospitals. For consistency, 2012 variables were renamed to match the format for corresponding elements from earlier years.

Study population:

We identified all 2003 to 2012 hospitalizations coded with a diagnosis of CDI. For case ascertainment, as specified in analyses[12], the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 008.45 (intestinal infection due to

CDI) was used. Analysis was done for all patients with a CDI code with a separate stratified analysis for those coded with either a primary or secondary CDI.

The database contains all primary and secondary CDI diagnoses, with the primary diagnoses representing the reason the patient was admitted to the hospital and the secondary diagnoses representing comorbidities and conditions acquired during the hospital stay. By convention, based on prior literature using this database, patients with a primary diagnosis of CDI were assumed to have had community-acquired CDI and patients with a secondary diagnosis of CDI were assumed to have had hospital-acquired CDI unless a symptom directly associated with CDI (abdominal pain, diarrhea) was listed as the primary diagnosis.[12] (See Table 1 for a comprehensive list of ICD-9-CM codes considered to be primary CDI).

Table 1: Principal diagnosis for primary CDI patients, according to ICD-9-CM

Diagnosis Code	Description
008.45	Intestinal infection due to CDI
276.5	Hypovolemia
578.9	Gastrointestinal hemorrhage NOS
560.1	Paralytic ileus
780.6	Fever
458.9	Hypotension NOS
578.1	Blood in stool
569.3	Rectal and anal hemorrhage
567.2	Other suppurative peritonitis
569.83	Perforation of intestine
780.2	Syncope and collapse
263.9	Protein-calorie malnutrition NOS
458.0	Orthostatic hypotension
555.9	Regional enteritis NOS
569.89	Intestinal disorders NEC
787.91	Diarrhea
276.8	Hypopotassemia
558.2	Toxic gastroenteritis
569.49	Rectal and anal disease NEC
789.00	Abdominal pain unspecified site
789.03	Abdominal pain right lower quadrant
789.04	Abdominal pain left lower quadrant
789.09	Abdominal pain other specified site
009.0	Infectious enteritis NOS
009.3	Diarrhea of infectious origin
262	Other severe malnutrition
263.8	Protein-calorie malnutrition NEC
458.2	Iatrogenic hypotension
458.8	Hypotension NEC
555.1	Regional enteritis, large intestine
567.8	Peritonitis NEC
567.9	Peritonitis NOS
569.82	Ulceration of intestine
579.8	Intestinal malabsorption NEC
780.79	Malaise and fatigue NEC
780.9	General symptoms NEC
783.0	Anorexia
789.07	Generalized abdominal pain

Note. NEC, not elsewhere classified; NOS, not otherwise specified.
Taken from (O'Brien, Lahue, Caro, & Davidson, 2007)[12]

Hospital and patient characteristics:

All statistical models were adjusted for the year of admission as well as patient-level characteristics, which included age, sex, the expected primary payer, socioeconomic status and patient comorbidities. The expected primary payer included (1) Medicare, (2) Medicaid, (3) Private Insurance, (4) Self-pay, (5) No charge, or (6) Other, i.e. Worker's compensation, CHAMPUS, CHAMPVA, Title V, and other government programs. As a proxy for patient's socioeconomic status, NIS provides a quartile classification of the estimated median household income of residents in the patient's zip code (Table 2). Since 20% of observations had a missing race value, race was not adjusted for in the model.

Table 2: Quartile income ranges for patient's zip code by year

(e.g. in 2012, a patient living in a zip code with a median income of $40,000 would be listed as Quartile 2)

Year	Quartile 1 ($)	Quartile 2 ($)	Quartile 3 ($)	Quartile 4 ($)
2003	1 - 35,999	36,000 - 44,999	45,000 - 59,999	60,000+
2004	1 - 35,999	36,000 - 44,999	45,000 - 58,999	59,000+
2005	1 - 36,999	37,000 - 45,999	46,000 - 60,999	61,000+
2006	1 - 37,999	38,000 - 46,999	47,000 - 61,999	62,000+
2007	1 - 38,999	39,000 - 47,999	48,000 - 62,999	63,000+
2008	1 - 38,999	39,000 - 48,999	49,000 - 63,999	64,000+
2009	1 - 39,999	40,000 - 49,999	50,000 - 65,999	66,000+
2010	1 - 40,999	41,000 - 50,999	51,000 - 66,999	67,000+
2011	1 - 38,999	39,000 - 47,999	48,000 - 63,999	64,000+
2012	1 - 38,999	39,000 - 47,999	48,000 - 62,999	63,000+

Patient comorbidities, including acquired immunodeficiency syndrome, lymphoma, metastatic cancer, solid tumor without metastasis, peptic ulcer disease, congestive heart failure, pulmonary circulatory disorders, chronic lung disease, collagen vascular disease, uncomplicated and complicated diabetes, liver disease, and chronic renal failure, were used in our statistical models to adjust for the patient population. Previous studies have shown that the strongest risk factors associated with CDI include prior antibiotic use, corticosteroid use, prior acid suppression, and multiple hospitalizations.[13] However, these data were not captured in the NIS. Therefore, we selected the patient comorbidities (those listed above) that were included in the NIS and most associated with prior antibiotic use, multiple hospitalizations, and other CDI risk factors.[14-16]

Hospital characteristics that were investigated included location (rural or urban), teaching status, region, hospital bed size, total discharges per hospital, whether a hospital was part of a multi-hospital system and classification of that hospital system. For the years between 2007 and 2010, we also investigated the relationship between CDI and the number of full time equivalents (FTE) of registered nurses (RN), licensed practical nurses (LPN), and nurse aides (CNA) per 1,000 adjusted inpatient days. The relationship between CDI and the percentage of RNs over all nurses (RNs and LPNs) was also investigated. (Table 3)

To account for regional variation in the amount of teaching hospitals, sensitivity analyses were done to compare CDI incidence rates, case-fatality rates, duration of hospitalization,

and total charges among all four regions (Northeast, Midwest, South, and West) with and without adjusting for the hospital teaching status.

Table 3: Hospital level risk factors

Hospital Characteristic	Description	Years available
Location	Classified as either located in rural or urban setting as classified by the CBSA codes.	2003 - 2012
Teaching Status	Classified as either teaching or nonteaching	2003 - 2012
Region	Region of the country of the hospital	2003 - 2012
Bed Size	Based on the number of hospital beds, hospital was categorized as small, medium, or large.	2003 - 2012
Multi-hospital system membership status	Indicates if the hospital is a member of a multi-hospital system	2003 - 2012
Multi-hospital system classification	Categorizes hospital system based on how much system centralizes hospital services, physician arrangements, and insurance products.	2003 - 2012
Total discharges	Total number of discharges in a hospital for the calendar year.	2003 - 2012
Percentage of RNs	Percentage of RN among all licensed nurses (RNs and LPNs).	2007 - 2010
Number of RN FTE	Number of RN FTE per 1000 adjusted inpatient days	2007 –2010
Number of LPN FTE	Number of LPN FTE per 1000 adjusted inpatient days	2007 –2010
Number of CNA FTE	Number of CNA per 1000 adjusted inpatient days	2007 - 2010

Hospital location:

The hospital-level factor for location classified each hospital as either located in a rural or urban setting. For the year 2003, this information pertained to the definition of Metropolitan Statistical Area according to the American Hospital Association Annual Survey of Hospitals, which used groups based on 1990 Census data. Beginning with 2004, the urban or rural classification was according to the newer Core Based Statistical Area (CBSA) codes, which were based on 2000 Census data. Hospitals in counties with a CBSA type of metropolitan were considered urban while other hospitals, including those designated as micropolitan, were considered rural. This change in 2004 resulted in a slight decline in the number of hospitals classified as rural instead of urban.

Hospital teaching status:

Hospitals were considered teaching if they had an American Medical Association approved residency program, were a member of the Council of Teaching Hospitals, or had a ratio of full-time equivalent interns and residents to beds of 0.25 or higher.

Hospital region:

Hospitals were divided by region according to the United States Census Bureau. The Northeast region included Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, and Pennsylvania. The Midwest region

included Ohio, Indiana, Illinois, Michigan, Wisconsin, Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, and Kansas. The South region included Delaware, Maryland, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida, Kentucky, Tennessee, Alabama, Mississippi, Arkansas, Louisiana, Oklahoma, Texas, and the District of Columbia. The West region included Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada, Washington, Oregon, California, Arkansas, and Hawaii.

Multi-hospital membership status and classification:

Two hospital variables HOSP_MHSMEMBER and HOSP_MHSCLUSTER regard to hospital membership in a multi-hospital system. HOSP_MHSMEMBER indicates if a hospital is part of a multi-hospital system. HOSP_MHSCLUSTER categorizes hospital systems based on how much the system differentiates its physician arrangements, insurance, and hospital services. Categories for HOSP_MHSCLUSTER include: (1) centralized health system, (2) centralized physician / insurance system, (3) moderately centralized health system, (4) decentralized hospital system, (5) independent hospital, or (6) not reported. These categories were only available for years 2007 through 2010, so only these years were analyzed for these two variables.

Number of beds in hospital:

The hospital bed size variable classifies hospitals as small, medium, or large based on the number of hospital beds. In order to ensure hospital and patient remain de-identified,

HCUP provides cutoffs for these categories that vary among region, hospital location (urban or rural status), as well as teaching status. (Table 4) Rural hospitals were not split according to teaching status because rural teaching hospitals were rare.

Table 4: Bedsize categories and cutoff values according to region, location, and teaching status. Taken from *http://www.hcupus.ahrq.gov/db/vars/hosp_bedsize/nisnote.jsp*.

BEDSIZE CATEGORIES			
Location and Teaching Status	Hospital Bedsize		
	Small	Medium	Large
NORTHEAST REGION			
Rural	1-49	50-99	100+
Urban, nonteaching	1-124	125-199	200+
Urban, teaching	1-249	250-424	425+
MIDWEST REGION			
Rural	1-29	30-49	50+
Urban, nonteaching	1-74	75-174	175+
Urban, teaching	1-249	250-374	375+
SOUTHERN REGION			
Rural	1-39	40-74	75+
Urban, nonteaching	1-99	100-199	200+
Urban, teaching	1-249	250-449	450+
WESTERN REGION			
Rural	1-24	25-44	45+
Urban, nonteaching	1-99	100-174	175+
Urban, teaching	1-199	200-324	325+

Total number of discharges per hospital:

The discharge variable refers to the total amount of discharges per hospital for a calendar year. In all statistical models analyzing this characteristic, increments of 1,000 discharges were used.

Nursing categories:

Several hospital characteristics regarding nursing were analyzed. The RN FTE variable includes the number of RN FTEs per 1,000 adjusted inpatient days. Inpatient days were adjusted by the ratio of outpatient to inpatient revenues because the RN FTEs reported to the AHA include both inpatient and outpatient services. Values were rounded to the nearest tenth and ranged from 0.1 to 10.9. The LPN FTE variable included the number of LPN FTE per 1000 adjusted inpatient days, with a range from 0 to 3.9. The CNA FTE variable included the number of CNA per 1000 adjusted inpatient days, with values ranging from 0 to 3.9. The RN percentage data element was the percentage of RNs among all licensed nurses (RNs and LPNs). Values were rounded to the nearest integer and range from 20 to 100.

Outcomes:

We analyzed the following outcomes: 1) CDI diagnosis in hospitalized patients, 2) In-hospital case fatality in patients with CDI 3) Duration of hospitalization for patients with CDI and 4) Total hospitalization charges for patients with CDI.

Table 5: Summary of data analysis

Aim	Subject group	Outcome / dependent variable	Independent variable	Analytic method
Aim 1 Rate	random sample of 5 million admissions	CDI	Used for all models year age gender primary payer income quartile AIDS lymphoma metastatic Ca solid tumor PUD CHF lung vasc dis lung struct dis CVD diabetes uncomp diabetes w comp liver disease renal failure	hierarchical logistic regression*
	random sample of 5 million admissions	primary CDI		hierarchical logistic regression*
	random sample of 5 million admissions	secondary CDI		hierarchical logistic regression*
Aim 2a Case fatality	all subjects with CDI	died during hospitalization		hierarchical logistic regression
	all subjects with primary CDI	died during hospitalization		hierarchical logistic regression
	all subjects with secondary CDI	died during hospitalization		hierarchical logistic regression
Aim 2b Length of Stay	all subjects with CDI	number of days of hospitalization**		hierarchical linear regression
	all subjects with primary CDI	number of days of hospitalization**		hierarchical linear regression
	all subjects with secondary CDI	number of days of hospitalization**		hierarchical linear regression
Aim 3 Total Charges	all subjects with CDI	total charges during hospitalization**		hierarchical linear regression
	all subjects with primary CDI	total charges during hospitalization**		hierarchical linear regression
	all subjects with secondary CDI	total charges during hospitalization**		hierarchical linear regression

*For hierarchical logistic regression modeling that accounted for hospital-level clustering of patients, we used generalized mixed models (PROC GLIMMIX) by incorporating patient-level and hospital-level variance. However, for our primary aim, if using the entire database, these procedures failed even when using the simplest hierarchical statistical models. Therefore, results were generated using samples of five million observations taken randomly.

**Log transformation was implemented to maintain linearity assumption.

Data analysis* (Table 5)*:

All data were analyzed using SAS/STAT® 9.3 TS Level 1M2 software. Generalized mixed models (PROC GLIMMIX) were used for all analyses. Generalized linear models (PROC MIXED) and other SAS procedures (PROC HPMIXED, PROC GENMOD, PROC GLM) were attempted but resulted in failure to converge or insufficient memory.

1. CDI occurrence - To identify hospital characteristics that were associated with the likelihood of CDI while adjusting for patient-level characteristics, we developed hierarchical models to account for hospital-level clustering. This was done using generalized mixed models (PROC GLIMMIX) where the intercept represented the residual baseline risk of CDI. As the full database was too large for the analysis to run, we used random samples of five million observations to run our hierarchical model, which we assumed to be representative of the whole population. To ensure that the random sample did not include any missing data, different random samples of five million observations had to be drawn for each hospital level characteristic investigated. Results were corroborated with a second random sample of five million observations. The covariance structure used for all models was compound-symmetry, which specifies that all the variances are equal and all the covariances are equal. The estimation method was specified as the maximum likelihood with Laplace approximation. These models examined three patient populations: 1) primary or secondary CDI together; 2) primary CDI*;* 3) secondary CDI. Patients with any missing variables were excluded from analysis.

2. Case fatality – As above, a hierarchical logistic regression using the random intercept model was used to analyze associations between each hospital-level factor and in-hospital death. Analysis were done for each hospital-level characteristic while adjusting for patient-level characteristics on database subsets containing only patients with a diagnosis of CDI (n = 644,765), primary CDI (n = 194,508) and a secondary discharge diagnosis of CDI (n = 450,257).

3. Duration of hospitalization – A hierarchical linear regression using a random intercept model clustered by hospitals was used to determine whether each hospital-level factor was associated with the duration of hospitalization of a patient with CDI. This was done using generalized mixed models (PROC GLIMMIX) specifying a Gaussian distribution. Quartile-residual plots between each hospital-level variable and the duration of hospitalization revealed non-linearity. After performing a log transformation using the log of the duration of hospitalization as the outcome, linearity was demonstrated for the relationship between the duration of hospitalization and each hospital-level variable. Patients who died in the hospital were excluded from this analysis as they were the sickest patients; they likely would have had the longest durations of hospitalization if they had lived.

4. **Total charges** – A hierarchical linear regression model similar to the model used for the duration of hospitalization was developed to determine whether there was an association between each hospital-level factor and the total amount of monetary charges

of a patient with CDI. This was done using generalized mixed models (PROC GLIMMIX) specifying a Gaussian distribution. Quartile-residual plots between each hospital-level variable and the total number of charges also revealed non-linearity. Therefore, we performed a log transformation using the log of total charges as the outcome to satisfy the linearity assumption of the model.

Human subjects protection:

Because the database consisted entirely of de-identified data, the Tufts Institutional Review Board granted a waiver that designated this study as not human subjects research. Data use agreements with the HCUP Central Distributor as well as certificates of online training for HCUP were signed by each author.

RESULTS

Baseline characteristics:

Table 6 shows the baseline characteristics for the patient population. The study population was mostly female (58%). In the total NIS database, the mean (± SD) age was 47.9 (27.9) years, while patients with CDI had a mean age of 67.9 (19.2) years. Thirty seven percent of patients had Medicare as their primary payer, while 34% had private insurance. Table 7 shows that most patients were admitted to urban (87%), non-teaching hospitals (54%) and hospitals that were part of a multi-hospital system (67%).

Baseline hospital characteristics are shown in Table 8. Most hospitals were urban (61%), non-teaching (83%), and members of a multi-hospital system (54%). The South had the majority of hospitals (39%) while the Northeast comprised only 13% of all participating hospitals. The average percentage of RNs (over all nursing staff) in each hospital was 85%.

Each year, there were five to seven million patients in the database. (Table 9) Between 55 cases and 99 cases (per 10,000 patients) had an ICD-9-CM diagnosis of CDI, with the percentage of CDI cases increasing each year. Secondary CDI diagnoses were more than twice as common as primary diagnoses each year.

Table 6: Comparison of the baseline characteristics of all patients in the database and those with an ICD-9-CM diagnosis of CDI (in percentage)

	All patients in the database n = 79,185,729	ALL CDI n = 644,765	1° CDI n = 194,508	2° CDI n = 450,257
Gender (%)				
**missing*	0.26	0.02	0.04	0.01
female	58.4	58.1	64.6	55.2
Age (mean ± SD)	47.9 (27.9)	67.9 (19.2)	67.9 (19.8)	67.9 (19.3)
Payer (%)				
**missing*	0.2	0.1	0.2	0.1
Medicare	37.4	68.5	68.1	68.7
Medicaid	19.6	8.7	7.2	9.3
Private (incl. HMO)	33.9	18.6	20.5	17.8
Self-pay	5.1	2.0	2.1	1.9
no charge	0.5	0.2	0.3	0.2
other	3.3	1.9	1.7	1.9
Zip Code Quartile (%)				
**missing*	2.4	2 .1	2.0	2.2
First	28.3	25.1	24.4	25.4
Second	25.2	24.2	24.9	23.9
Third	23.2	24.5	24.8	24.4
Fourth	20.9	24.0	24.0	24.1
% with Comorbidities (%)				
Rheumatoid Arthritis	1.8	3.5	4.2	3.2
Congestive Heart Failure	6.4	20.0	17.0	21.7
Renal Failure	6.9	19.6	17.2	20.6
Chronic Lung Disease	14.2	24.0	22.7	24.6
Pulmonary circulation d/o	1.1	3.2	2.5	3.6
Diabetes – uncomplicated	14.0	19.4	18.8	19.6
Diabetes – complicated	3.1	6.7	5.4	7.2
Liver disease	1.8	3.7	3.6	3.8
Cancer with metastasis	1.6	3.6	3.3	3.8
Solid tumor	1.5	3.7	3.7	3.5
Lymphoma	0.6	1.9	1.8	2.0
Peptic ulcer disease	0.03	0.06	0.07	0.06
HIV/AIDS	0.2	0.5	0.7	0.4

Table 7: Comparison of the number of discharges in database per hospital level characteristic in all patients in the database and those with an ICD-9-CM diagnosis of CDI (in percentage)

	All patients in the database n = 79,185,729	All CDI n = 644,765	1° CDI n = 194,508	2° CDI n = 450,257
Location (%)				
Rural	12	10	13	8
Urban	87	90	87	92
Teaching Status (%)				
Non-teaching	54	52	58	50
Teaching	46	48	42	50
Region (%)				
West	20	17	16	18
South	39	35	37	34
Midwest	22	25	25	24
Northeast	19	23	22	24
Multi-hospital System Membership (%)				
Non-MHS Member	33	30	32	29
MHS Member	67	70	68	71
Health System Classification (%)				
Centralized	16	17	17	17
Centr. Physicians./ Ins.	8	9	8	9
Moderately Centralized	32	30	31	30
Decentralized	35	32	35	31
Independent	6	9	6	10
Blank	3	3	3	3
Bed Size (%)				
Small	13	14	14	14
Medium	25	23	25	23
Large	62	63	61	63

Table 8: Baseline hospital characteristics

Hospital Characteristic (n = #hospitals analyzed)		Hospitals
Location (%)		
(n = 4,079)		
	Rural	39
	Urban	61
Teaching Status (%)		
(n = 4,079)		
	Non-teaching	83
	Teaching	17
Region (%)		
(n = 4,093)		
	West	19
	South	39
	Midwest	29
	Northeast	13
Multi-hospital System Membership (%)		
(n = 1,097)		
	Non-MHS Member	44
	MHS Member	56
Health System Classification (%)		
(n = 1,061)		
	Centralized	9
	Centr. Physicians./ Ins.	6
	Moderately Centralized	26
	Decentralized	36
	Independent	16
	Blank	7
Bed Size (%)		
(n = 1,097)		
	Small	43
	Medium	26
	Large	31
Total Number of Discharges per Hospital (mean ± SD)		7,682 (9,823)
(n = 4,093)		
Percentage of RNs among all nurses (mean ± SD)		85% (13%)
(n = 1,920)		
Number of RN FTE per 1,000 patient days (mean ± SD)		3.3 (1.7)
(n =1,925)		
Number of LPN FTE per 1,000 patient days (mean ± SD)		0.5 (0.5)
(n = 1,949)		
Number of CAN FTE per 1,000 patient days (mean ± SD)		1.0 (0.6)
(n = 1,931)		

Table 9: Number of patients of each year analyzed

Year	Total Pts	Total CDI	% with CDI	1° CDI	2° CDI
2003	7,977,728	43,531	0.55%	10,176	33,355
2004	8,004,571	50,747	0.63%	12,405	38,342
2005	7,995,048	61,369	0.77%	15,553	45,816
2006	8,074,825	64,668	0.80%	18,341	46,327
2007	8,043,415	65,351	0.81%	20,970	44,381
2008	8,158,381	71,026	0.87%	23,201	47,825
2009	7,810,762	66,623	0.85%	21,837	44,786
2010	7,800,441	69,315	0.89%	22,329	46,986
2011	8,023,590	79,633	0.99%	25,814	53,819
2012	7,296,968	72,502	0.99%	23,882	48,620
Total	**79,185,729**	**644,765**	**0.81%**	**194,508**	**450,257**

***Odds of having a CDI diagnosis*: (Figures 1 & 2, Tables 10 & 11)**

Urban hospitals, as opposed to rural hospitals, had a 53%,and 91% increased odds of having a diagnosis of CDI and secondary diagnosis of CDI, respectively. Teaching hospitals had a 25% increased odds of CDI in comparison with nonteaching hospitals and a 38% increased odds of secondary CDI. The Northeast had a more than 10% increased odds of having a patient with a diagnosis of CDI and secondary discharge diagnosis of CDI compared to other regions of the country, even after adjusting for hospital teaching status. The Northeast also showed increased odds of having a patient with a primary CDI diagnosis as compared to the South and West regions, with and without adjusting for hospital teaching status (Table 19 & 20). (Separate analyses were done using both the West and Northeast as the reference – Tables 20 & 21). Members of a multi-hospital system did not show any significant difference in odds of having any CDI diagnosis. Independent hospitals had the highest odds whereas decentralized hospitals had the lowest odds of CDI and secondary CDI. Independent hospitals though had the lowest odds of primary CDI. The size of the hospital was not significantly associated with the odds of any CDI diagnosis.

There were increased odds of having a CDI and secondary CDI diagnosis for each additional unit of 1,000 discharges and CNA FTE. However, each additional LPN FTE decreased the odds of CDI, primary CDI, and secondary CDI by 4%, 11%, and 3%, respectively.

Figure 1: Odds Ratio for the likelihood of a patient with a CDI diagnosis in a hospital with each of the following characteristics versus a hospital with the reference characteristic

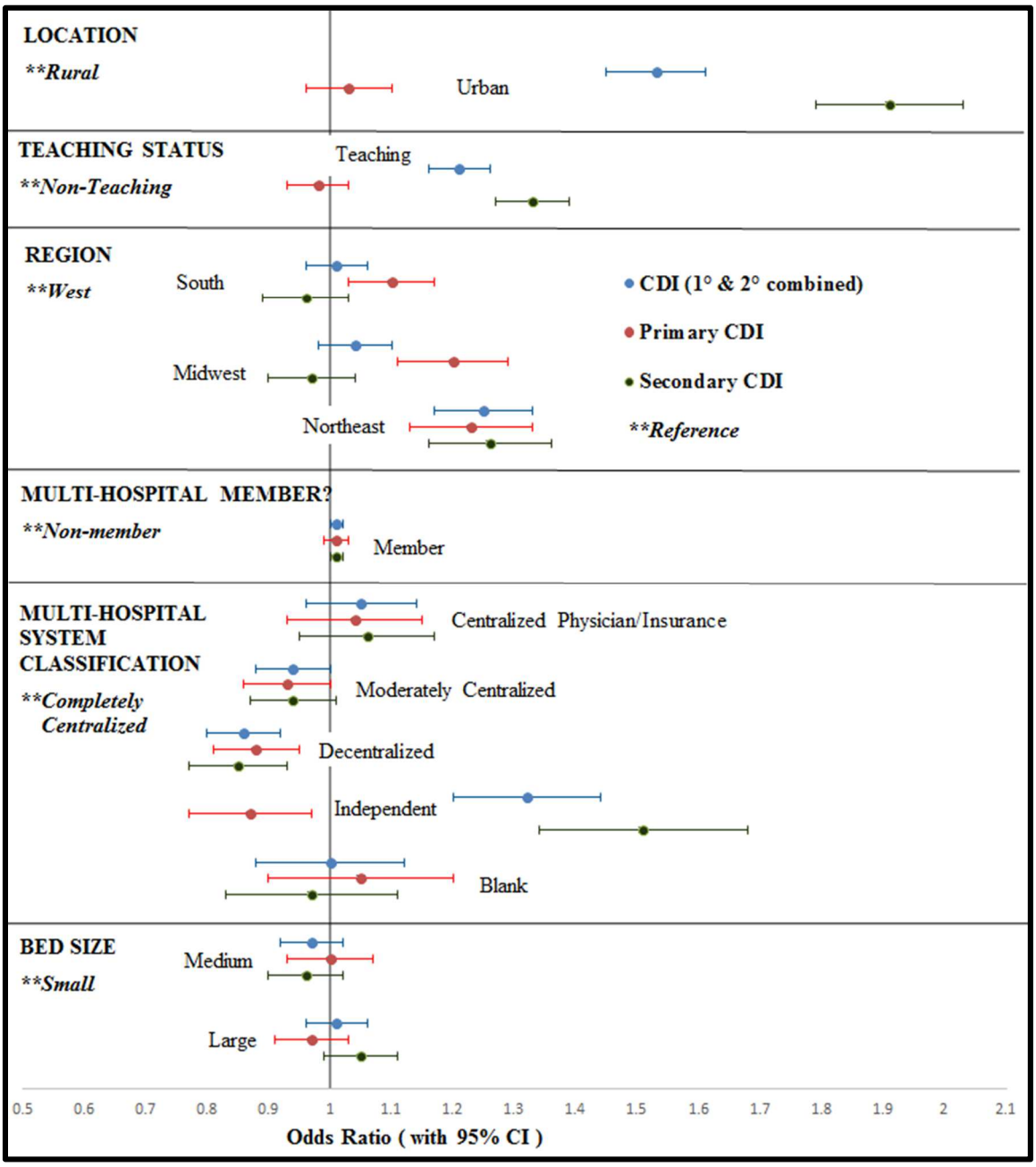
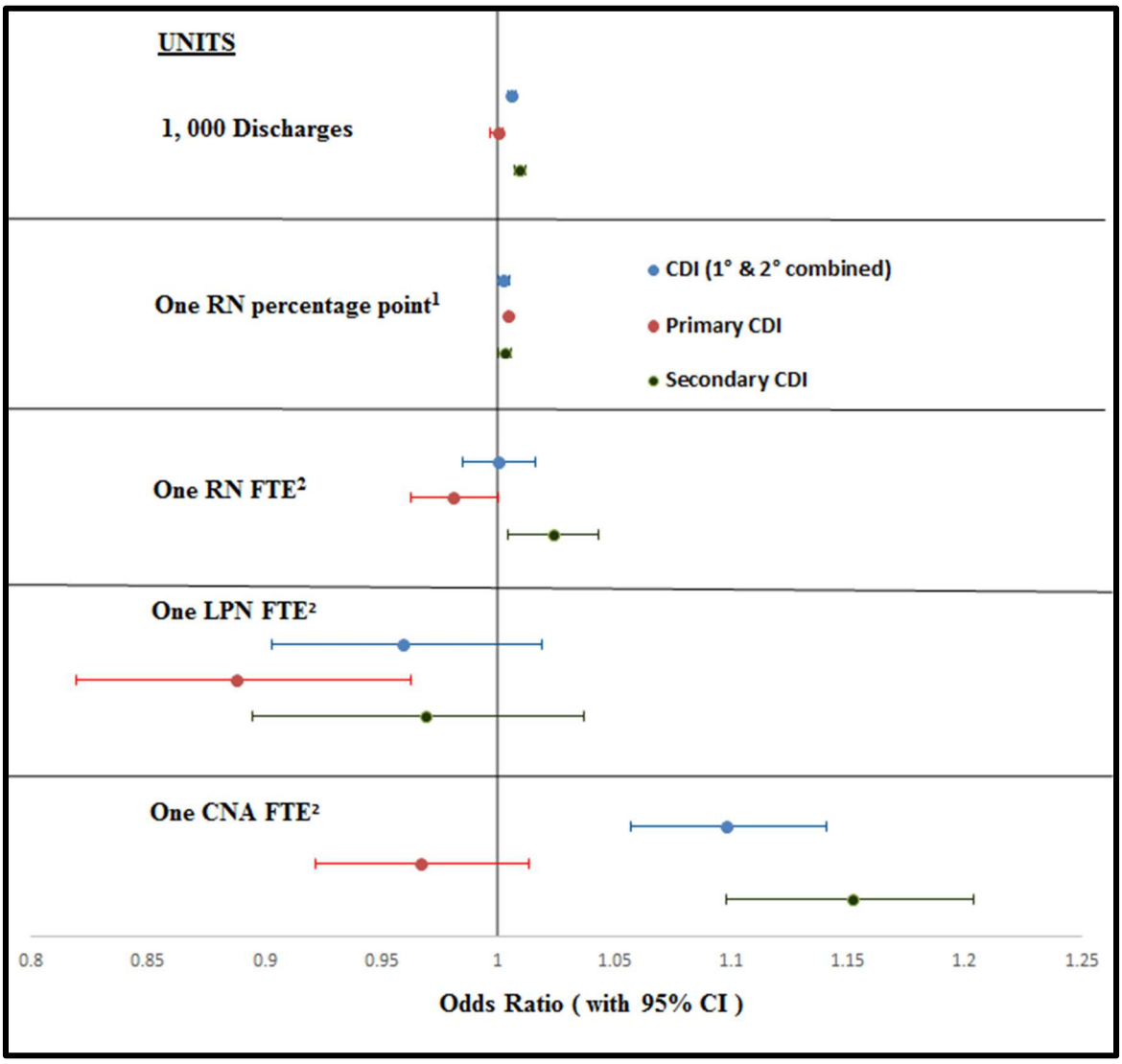


Table 10: Odds Ratio for the likelihood of a patient with a CDI diagnosis in a hospital with each of the following characteristics versus a hospital with the reference characteristic

	All CDI (95% CI)	1° CDI (95% CI)	2° CDI (95% CI)
Location			
Rural	Reference	Reference	Reference
Urban	1.53 (1.45, 1.61)	1.03 (0.96, 1.10)	1.91 (1.79, 2.04)
Teaching Status			
Nonteaching	Reference	Reference	Reference
Teaching	1.21 (1.16, 1.26)	0.98 (0.93, 1.03)	1.33 (1.27, 1.40)
Region			
West	Reference	Reference	Reference
South	1.01 (0.96, 1.08)	1.10 (1.03, 1.19)	0.96 (0.89, 1.03)
Midwest	1.04 (0.98, 1.10)	1.20 (1.11, 1.29)	0.97 (0.90, 1.04)
Northeast	1.25 (1.17, 1.33)	1.23 (1.13, 1.33)	1.26 (1.16, 1.37)
Multi-hospital Member?			
Non-MHS Member	Reference	Reference	Reference
MHS Member	1.01 (1.00, 1.02)	1.01 (0.99, 1.02)	1.01 (1.00, 1.02)
Health System Classification			
Centralized	Reference	Reference	Reference
Centr. Physicians./ Ins.	1.05 (0.96, 1.15)	1.04 (0.93, 1.17)	1.06 (0.95, 1.18)
Moderately Centralized	0.94 (0.88, 1.00)	0.93 (0.86, 1.01)	0.94 (0.87, 1.02)
Decentralized	0.86 (0.80, 0.93)	0.88 (0.81, 0.95)	0.85 (0.77, 0.92)
Independent	1.32 (1.20, 1.46)	0.87 (0.77, 0.98)	1.51 (1.34, 1.70)
Blank	1.00 (0.88, 1.14)	1.05 (0.90, 1.22)	0.97 (0.83, 1.14)
Bed size			
Small	Reference	Reference	Reference
Medium	0.97 (0.92, 1.02)	1.00 (0.93, 1.08)	0.96 (0.90, 1.02)
Large	1.01 (0.96, 1.06)	0.97 (0.91, 1.04)	1.05 (0.99, 1.11)

Figure 2: Odds Ratio for the likelihood of a patient with a CDI diagnosis in a hospital with one more unit (e.g. 1,000 more discharges, one more percentage of RNs) relative to another hospital



[1]Percentage of RN over total number of all nurses (RNs and LPNs)

[2]FTE refers to 1 full time equivalent per 1,000 adjusted inpatient days

Table 11: Odds Ratio for the likelihood of a patient with a CDI diagnosis in a hospital with one more unit (e.g. 1,000 more discharges, one more percentage of RNs) relative to another hospital

Unit	All CDI (95% CI)	1° CDI (95% CI)	2° CDI (95% CI)
1,000 discharges	1.006 (1.004, 1.008)	1.000 (0.997, 1.002)	1.009 (1.006, 1.011)
One RN percentage point[1]	1.002 (1.000, 1.005)	1.004 (1.004, 1.004)	1.003 (1.000, 1.006)
One RN FTE[2]	1.000 (0.985, 1.016)	0.981 (0.963, 1.000)	1.024 (1.005, 1.044)
One LPN FTE[2]	0.959 (0.903, 1.019)	0.888 (0.819, 0.963)	0.969 (0.901, 1.043)
One CNA FTE[2]	1.098 (1.057, 1.141)	0.967 (0.922, 1.013)	1.152 (1.100, 1.206)

[1]Percentage of RN over total number of all nurses (RNs and LPNs)

[2]FTE refers to 1 full time equivalent per 1,000 adjusted inpatient days

***Odds of dying in the hospital with CDI*: (Figures 3 & 4, Tables 12 & 13)**

Patients admitted to urban, as compared with rural, hospitals had a 36% and a 25% increased odds of dying in the hospital among those with a diagnosis of CDI and secondary CDI, respectively. Patients admitted to teaching hospitals had a 12% and a 7% increased odds of dying in the hospital among patients with CDI and secondary CDI, respectively. The Northeast had the highest case rates of dying in the hospital for CDI, primary CDI, and secondary CDI, while hospitals in the Midwest had the lowest rates of dying with CDI and secondary CDI. This regional variability was similar after adjusting for hospital teaching status. Patients admitted to independent hospitals had much higher odds of CDI (31%), primary CDI (31%), and secondary CDI (18%) associated death compared with centralized hospitals.

There was a significant increase in the odds of dying among those with CDI for each additional unit of 1,000 discharges. There was also a significant association between the odds of dying in the hospital and having a CDI diagnosis for each additional RN FTE and CNA FTE. There were no significant associations found for each additional LPN or an increase the percentage of RNs.

Figure 3: Odds Ratio for the likelihood of dying with CDI in a hospital with each of the following characteristics versus a hospital with the reference characteristic

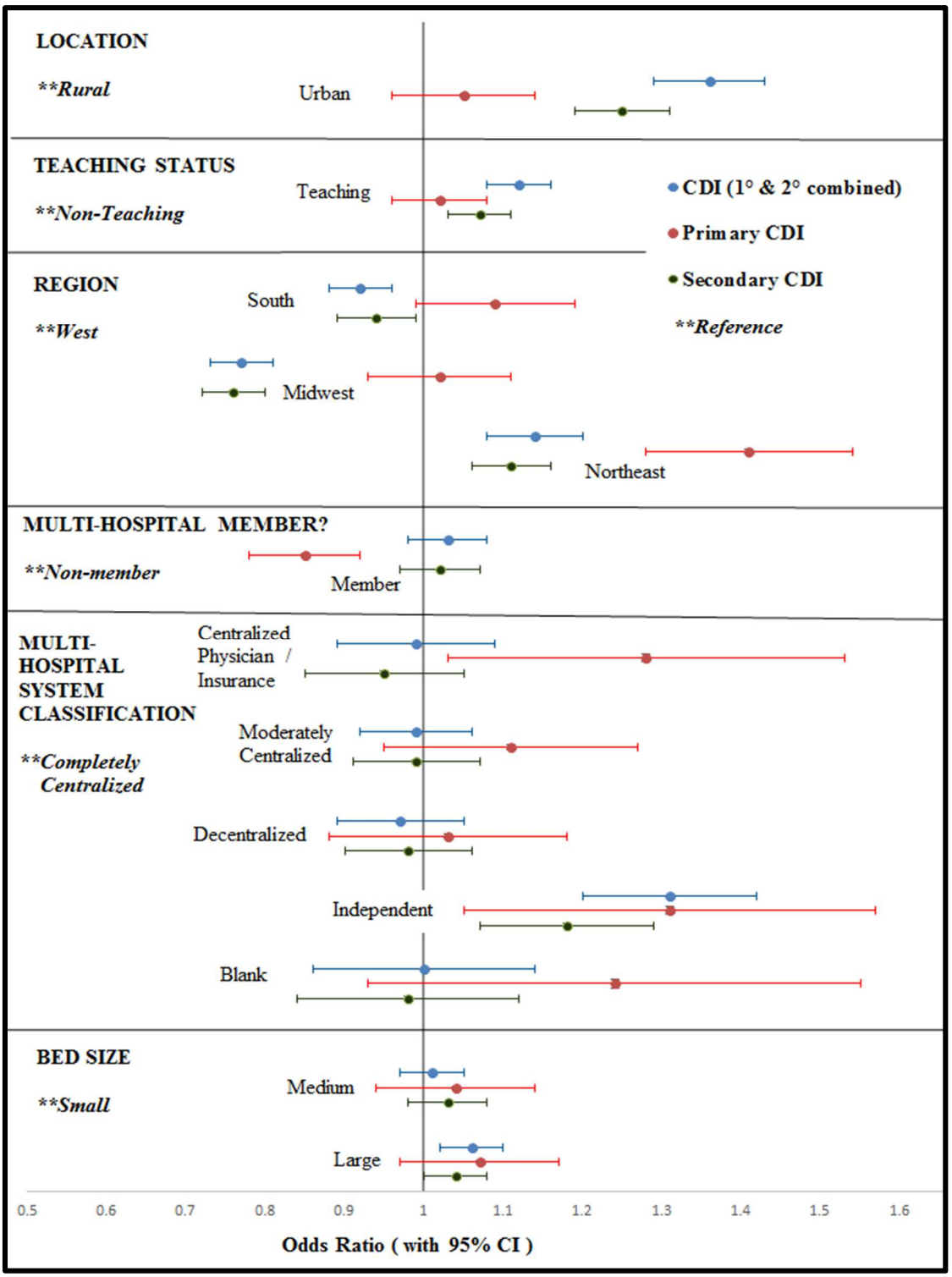
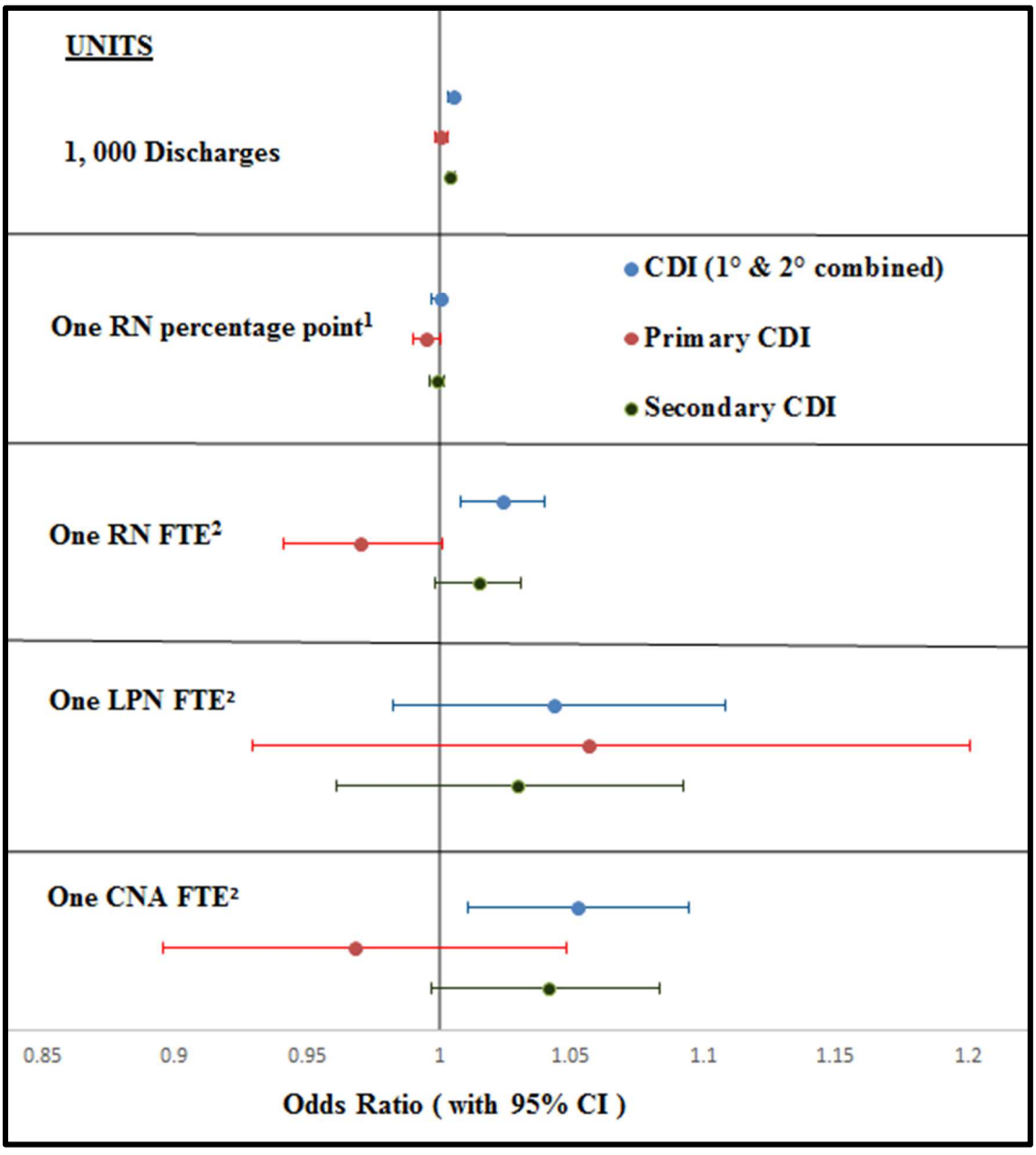


Table 12: Odds Ratio for the likelihood of dying with CDI in a hospital with each of the following characteristics versus a hospital with the reference characteristic

	All CDI (95% CI)	1° CDI (95% CI)	2° CDI (95% CI)
Location			
Rural	Reference	Reference	Reference
Urban	1.36 (1.29, 1.42)	1.05 (0.96, 1.15)	1.25 (1.19, 1.32)
Teaching Status			
Nonteaching	Reference	Reference	Reference
Teaching	1.12 (1.08, 1.16)	1.02 (0.96, 1.09)	1.07 (1.03, 1.10)
Region			
West	Reference	Reference	Reference
South	0.92 (0.88, 0.97)	1.09 (0.99, 1.20)	0.94 (0.89, 0.98)
Midwest	0.77 (0.73, 0.81)	1.02 (0.93, 1.13)	0.76 (0.72, 0.80)
Northeast	1.14 (1.08, 1.20)	1.41 (1.28, 1.55)	1.11 (1.06, 1.17)
Multi-hospital Member?			
Non-MHS Member	Reference	Reference	Reference
MHS Member	1.03 (0.98, 1.08)	0.85 (0.78, 0.92)	1.02 (0.97, 1.08)
Health System Classification			
Centralized	Reference	Reference	Reference
Centr. Physicians./ Ins.	0.99 (0.89, 1.11)	1.28 (1.03, 1.59)	0.95 (0.85, 1.06)
Moderately Centralized	0.99 (0.92, 1.07)	1.11 (0.95, 1.30)	0.99 (0.91, 1.07)
Decentralized	0.97 (0.89, 1.05)	1.03 (0.88, 1.20)	0.98 (0.90, 1.06)
Independent	1.31 (1.20, 1.45)	1.31 (1.05, 1.63)	1.18 (1.07, 1.30)
Blank	1.00 (0.86, 1.15)	1.24 (0.93, 1.65)	0.98 (0.84, 1.14)
Bed size			
Small	Reference	Reference	Reference
Medium	1.01 (0.97, 1.06)	1.04 (0.94, 1.14)	1.03 (0.98, 1.08)
Large	1.06 (1.02, 1.10)	1.07 (0.97, 1.18)	1.04 (1.00, 1.09)

Figure 4: Odds Ratio for the likelihood of dying with CDI in a hospital with one more unit (e.g. 1,000 more discharges, one more RN percentage point) relative to another hospital



[1]Percentage of RN over total number of all nurses (RNs and LPNs)

[2]FTE refers to 1 full time equivalent per 1,000 adjusted inpatient days

Table 13: Odds Ratio for the likelihood of dying with CDI in a hospital with one more unit (e.g. 1,000 more discharges, one more RN percentage point) relative to another hospital

Unit	All CDI (95% CI)	1° CDI (95% CI)	2° CDI (95% CI)
1,000 discharges	1.005 (1.003, 1.006)	1.000 (0.998, 1.003)	1.004 (1.002, 1.005)
One RN percentage point[1]	1.000 (0.997, 1.002)	0.995 (0.990, 1.000)	0.999 (0.996, 1.002)
One RN FTE[2]	1.024 (1.008, 1.040)	0.970 (0.941, 1.001)	1.015 (0.999, 1.032)
One LPN FTE[2]	1.043 (0.982, 1.108)	1.056 (0.929, 1.201)	1.029 (0.966, 1.097)
One CNA FTE[2]	1.052 (1.011, 1.094)	0.968 (0.895, 1.048)	1.041 (0.999, 1.085)

[1]Percentage of RN over total number of all nurses (RNs and LPNs)

[2]FTE refers to 1 full time equivalent per 1,000 adjusted inpatient days

***Duration of hospitalization*: (Figures 5 & 6, Tables 14 & 15)**

Longer durations of hospitalizations for CDI, primary CDI, and secondary CDI were associated with urban and teaching hospitals. The Northeast had the longest while the Midwest had the shortest durations of hospitalization, with and without adjusting for hospital teaching status. Multi-hospital membership was associated with a longer duration of hospitalization for patients with CDI, primary CDI, or secondary CDI. Independent hospitals were associated with the longest duration of hospitalization. The size of the hospital and an increase in the number of discharges were associated with patients with longer durations of hospitalization with large hospitals having the longest duration.

The addition of one LPN or one CNA was associated with longer durations of hospitalization for all CDI categories. An increase in the percentage of RNs over all nurses (LPNs and RNs) was associated with shorter hospital durations for patients with CDI or secondary CDI; although an increase in the total number of RN FTE was associated with a longer duration of hospitalization for patients with CDI or secondary CDI.

Figure 5: Percent difference in the average duration of hospitalization for patients with CDI admitted to a hospital with each of the following characteristics versus a hospital with the reference characteristic

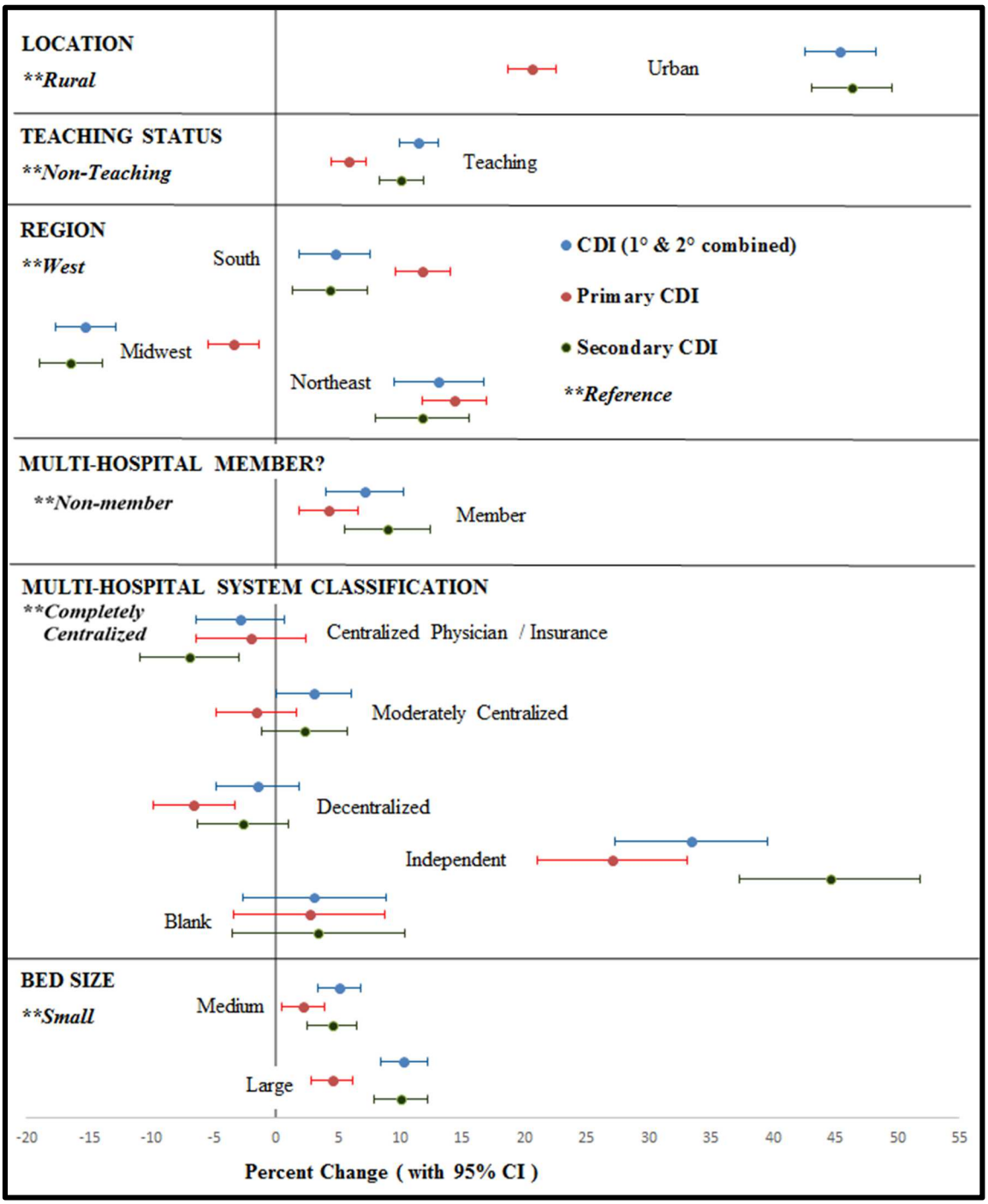
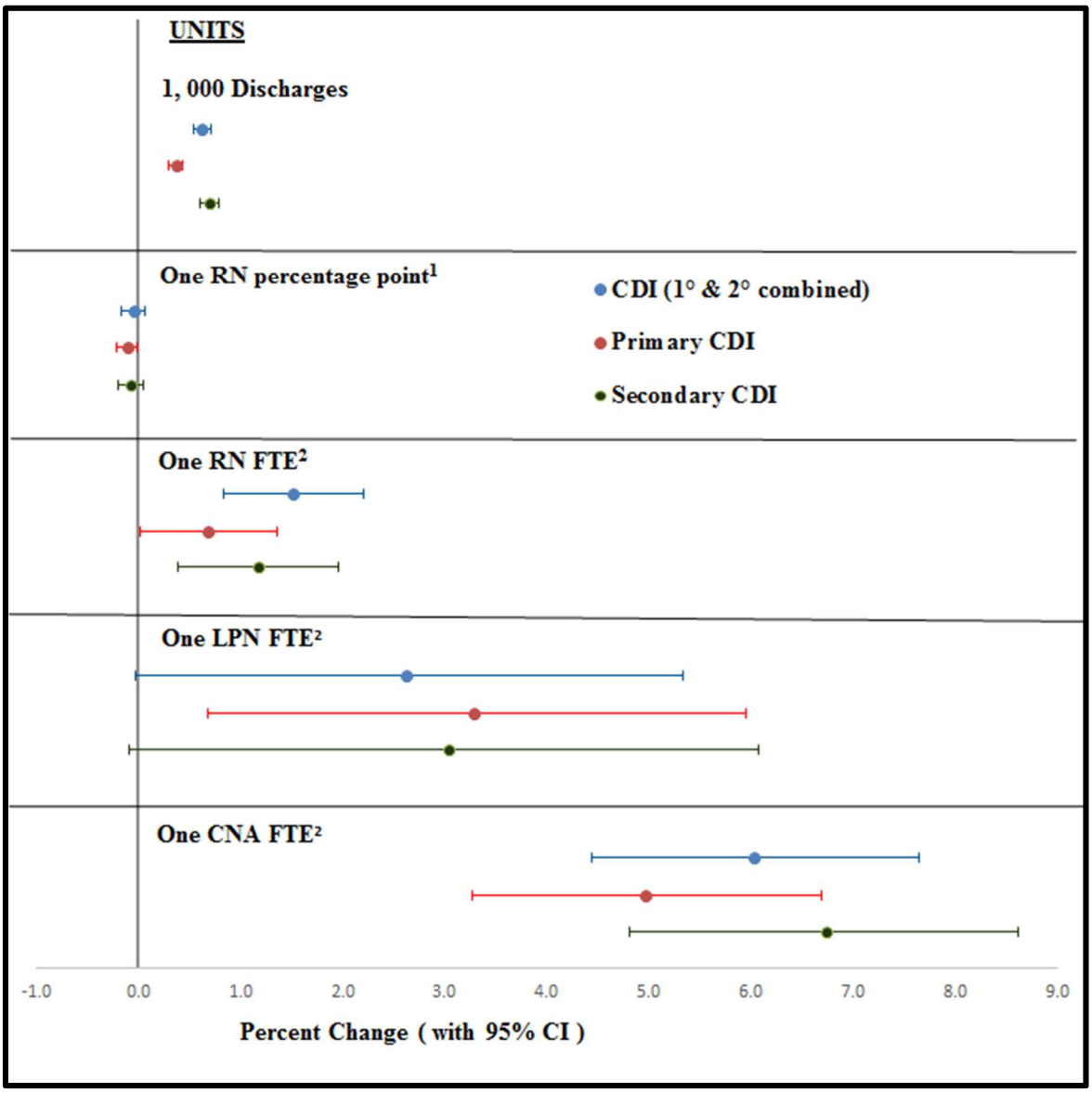


Table 14: Percent difference in the average duration of hospitalization for patients with CDI admitted to a hospital with each of the following characteristics versus a hospital with the reference characteristic

	All CDI (95% CI)	1° CDI (95% CI)	2° CDI (95% CI)
Location			
Rural	Reference	Reference	Reference
Urban	46% (43%, 49%)	21% (19%, 23%)	46% (43%, 50%)
Teaching Status			
Nonteaching	Reference	Reference	Reference
Teaching	12% (10%, 13%)	6% (5%, 8%)	11% (9%, 12%)
Region			
West	Reference	Reference	Reference
South	4% (1%, 6%)	12% (9%, 14%)	2 (-1%, 5%)
Midwest	-16% (-19%, -14%)	-4% (-6%, -2%)	-16% (-18%, -13%)
Northeast	13% (10%, 17%)	15% (12%, 17%)	12% (8%, 15%)
Multi-hospital Member?			
Non-MHS Member	Reference	Reference	Reference
MHS Member	7% (4%, 10%)	4% (2%, 6%)	8% (4%, 11%)
Health System Classification			
Centralized	Reference	Reference	Reference
Centr. Physicians./ Ins.	-4% (-7%, 0%)	-3% (-7%, 2%)	-7% (-11%, -3%)
Moderately Centralized	4% (1%, 7%)	-2% (-5%, 2%)	3% (-1%, 6%)
Decentralized	-2% (-5%, 2%)	-7% (-10%, -3%)	-2% (-5%, 2%)
Independent	33% (27%, 40%)	26% (20%, 33%)	40% (33%, 48%)
Blank	1% (-4%, 7%)	1% (-5%, 7%)	3% (-4%, 10%)
Bed size			
Small	Reference	Reference	Reference
Medium	4% (3%, 6%)	2% (0%, 4%)	4% (2%, 6%)
Large	10% (8%, 12%)	4% (3%, 6%)	10% (8%, 12%)

Figure 6: Percent difference in the average duration of hospitalization for a patient in a hospital with one more unit (e.g. 1,000 more discharges, one more RN percentage point) relative to another hospital



[1]Percentage of RN over total number of all nurses (RNs and LPNs)

[2]FTE refers to 1 full time equivalent per 1,000 adjusted inpatient days

Table 15: Percent difference in the average duration of hospitalization for a patient in a hospital with one more unit (e.g. 1,000 more discharges, one more RN percentage point) relative to another hospital

Unit	All CDI (95% CI)	1° CDI (95% CI)	2° CDI (95% CI)
1,000 discharges	0.7% (0.6%, 0.8%)	0.4% (0.3%, 0.5%)	0.7% (0.6%, 0.8%)
One RN percentage point[1]	-0.2% (-0.3%, -0.1%)	-0.1% (-0.2%, 0.1%)	-0.3% (-0.4%, -0.2%)
One RN FTE[2]	1.2% (0.6%, 1.9%)	0.7% (0.0%, 1.4%)	0.9% (0.2%, 1.7%)
One LPN FTE[2]	5.4% (2.7%, 8.2%)	3.5% (0.9%, 6.2%)	4.9% (1.8%, 8.0%)
One CNA FTE[2]	5.6% (4.1%, 7.3%)	4.9% (3.2%, 6.6%)	6.4% (4.5%, 8.3%)

[1]Percentage of RN over total number of all nurses (RNs and LPNs)

[2]FTE refers to 1 full time equivalent per 1,000 adjusted inpatient days

***Total hospital charges*: (Figures 7 & 8, Tables 16 & 17)**

Compared with patients admitted to rural hospitals, urban hospitals had higher total charges for CDI (84%), primary CDI (62%), and secondary CDI (84%). Teaching hospitals had 9% to 11% higher total charges compared to nonteaching hospitals among all CDI, primary CDI, and secondary CDI. Northeast hospitals had much higher charges than the other regions of the United States, with and without adjusting for hospital teaching status. Membership in a multi-hospital system had 8% higher total charges for secondary CDI over solo hospitals. Total charges also increased going from small to medium to large hospitals for all three CDI categories. An increase of 1,000 discharges and an increase in RN FTE were associated with a significant increase in total charges for CDI, primary CDI, and secondary CDI.

Figure 7: Percent difference in the average total hospital charges for a patient with CDI admitted to a hospital with each of the following characteristics versus a hospital with the reference characteristic

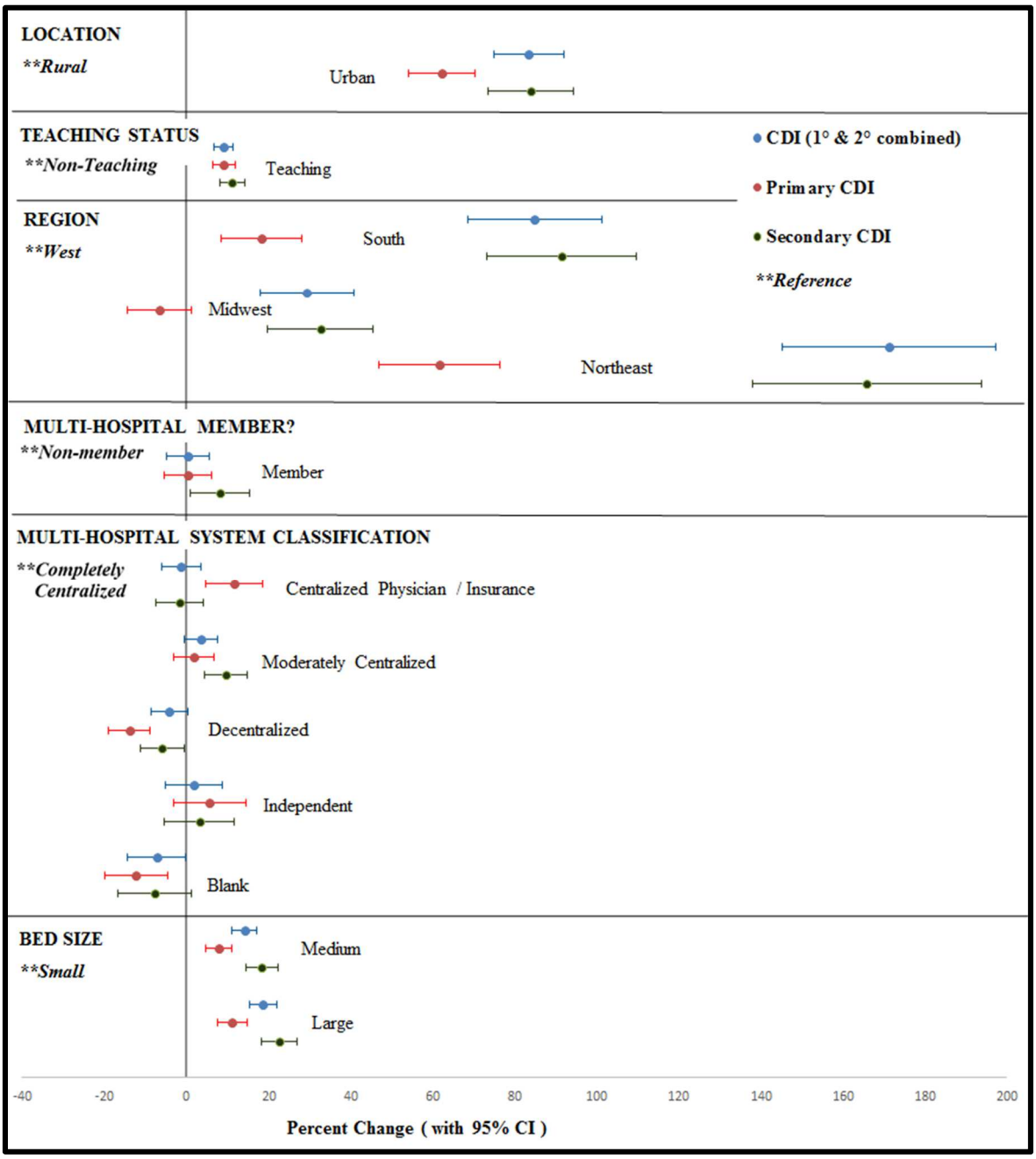
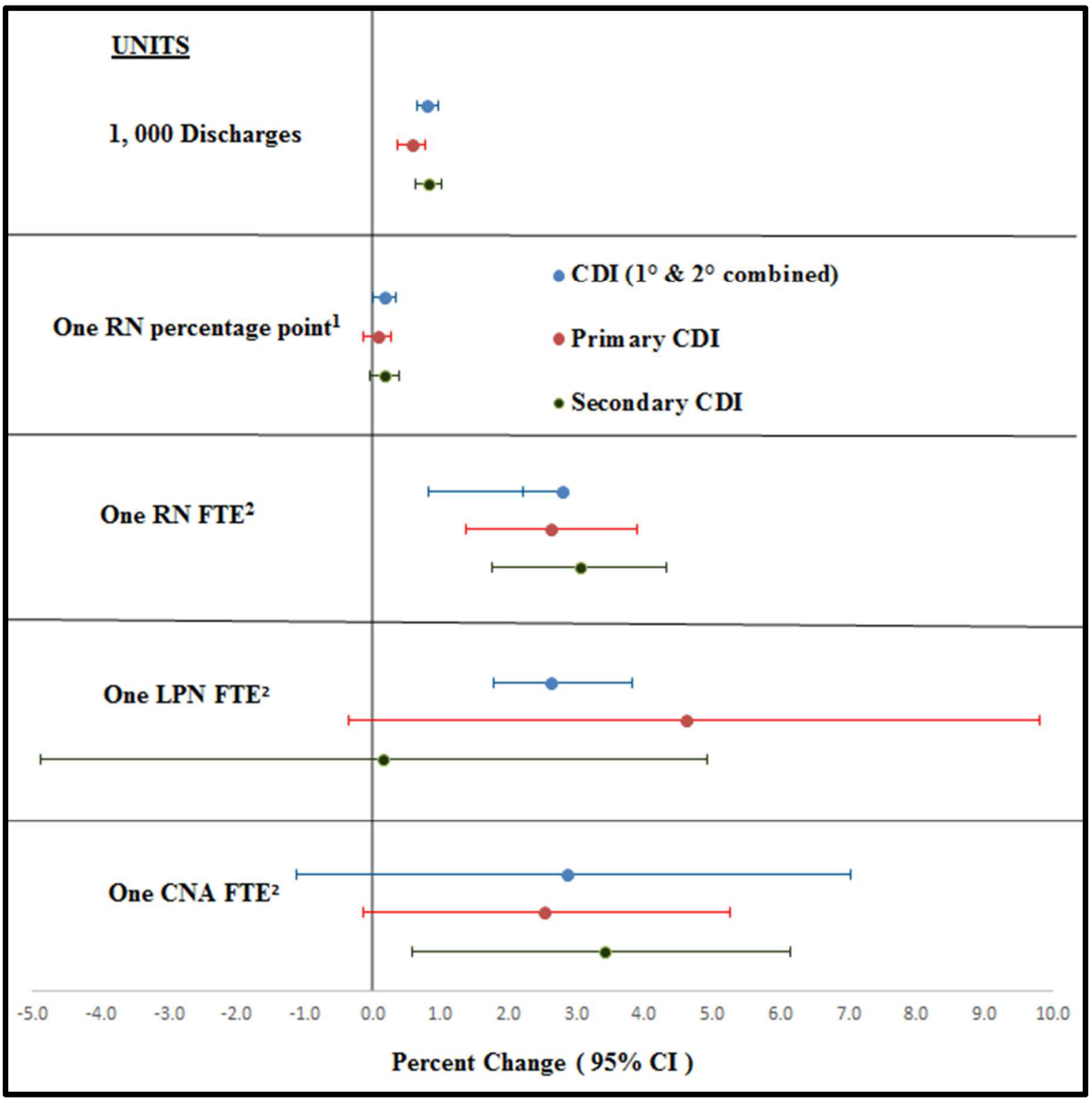


Table 16: Percent difference in the average total hospital charges for a patient with CDI admitted to a hospital with each of the following characteristics versus a hospital with the reference characteristic

	All CDI (95% CI)	1° CDI (95% CI)	2° CDI (95% CI)
Location			
Rural	Reference	Reference	Reference
Urban	84% (75%, 93%)	62% (54%, 71%)	84% (74%, 95%)
Teaching Status			
Nonteaching	Reference	Reference	Reference
Teaching	9% (7%, 11%)	9% (6%, 12%)	11% (8%, 14%)
Region			
West	Reference	Reference	Reference
South	85% (69%, 103%)	18% (9%, 29%)	91% (73%, 111%)
Midwest	29% (18%, 42%)	-7% (-14%, 2%)	33% (20%, 47%)
Northeast	171% (145%, 200%)	32% (47%, 78%)	166% (138%, 197%)
Multi-hospital Member?			
Non-MHS Member	Reference	Reference	Reference
MHS Member	0% (-5%, 6%)	0% (-6%, 7%)	8% (1%, 15%)
Health System Classification			
Centralized	Reference	Reference	Reference
Centr. Physicians./ Ins.	-1% (-6%, 4%)	12% (5%, 19%)	-2% (-7%, 4%)
Moderately Centralized	4% (0%, 8%)	2% (-3%, 7%)	10% (4%, 15%)
Decentralized	-4% (-9%, 1%)	-14% (-19%, -8%)	-6% (-11%, 0%)
Independent	2% (-5%, 9%)	6% (-3%, 15%)	3% (-5%, 12%)
Blank	-7% (-14%, 0%)	-12% (-20%, -4%)	-8% (-17%, 2%)
Bed size			
Small	Reference	Reference	Reference
Medium	14% (11%, 17%)	8% (5%, 11%)	18% (14%, 22%)
Large	19% (15%, 22%)	11% (8%, 15%)	23% (18%, 27%)

Figure 8: Percent difference in the average total hospital charges for a patient with CDI in a hospital with one more unit (e.g. 1,000 more discharges, one more RN percentage point) relative to another hospital



[1]Percentage of RN over total number of all nurses (RNs and LPNs)

[2]FTE refers to 1 full time equivalent per 1,000 adjusted inpatient days

Table 17: Percent difference in the average total hospital charges for a patient with CDI in a hospital with one more unit (e.g. 1,000 more discharges, one more RN percentage point) relative to another hospital

Unit	All CDI (95% CI)	1° CDI (95% CI)	2° CDI (95% CI)
1,000 discharges	0.8% (0.7%, 1.0%)	0.6% (0.4%, 0.8%)	0.8% (0.6%, 1.0%)
One RN percentage point[1]	0.2% (0.0%, 0.4%)	0.1% (-0.1%, 0.3%)	0.2% (0.0%, 0.4%)
One RN FTE[2]	2.8% (1.8%, 3.8%)	2.6% (1.4%, 3.9%)	3.1% (1.8%, 4.3%)
One LPN FTE[2]	2.9% (-1.1%, 7.0%)	4.6% (-0.3%, 9.8%)	0.2% (-4.6%, 5.2%)
One CNA FTE[2]	3.1% (1.0%, 5.4%)	2.5% (-0.1%, 5.3%)	3.4% (0.7%, 6.2%)

[1]Percentage of RN over total number of all nurses (RNs and LPNs)

[2]FTE refers to 1 full time equivalent per 1,000 adjusted inpatient days

Table 18: Odds ratios for having a CDI diagnosis and for dying with CDI according to region with West as the reference *adjusted for hospital teaching status*

Region (adjusted)	All patients with CDI (95% CI)		1° CDI (95% CI)		2° CDI (95% CI)	
Odds of CDI	West	Reference	West	Reference	West	Reference
	South	0.98 (0.92, 1.04)	South	1.06 (0.98, 1.13)	South	0.94 (0.88, 1.01)
	Midwest	1.01 (0.95, 1.08)	Midwest	1.17 (1.08, 1.26)	Midwest	0.94 (0.87, 1.01)
	Northeast	1.19 (1.11, 1.27)	Northeast	1.27 (1.17, 1.37)	Northeast	1.16 (1.07, 1.26)
Case fatality	West	Reference	West	Reference	West	Reference
	South	0.94 (0.89, 0.99)	South	1.05 (0.94, 1.18)	South	0.94 (0.89, 0.99)
	Midwest	0.78 (0.74, 0.83)	Midwest	1.03 (0.91, 1.15)	Midwest	0.78 (0.74, 0.83)
	Northeast	1.12 (1.07, 1.19)	Northeast	1.38 (1.18, 1.61)	Northeast	1.12 (1.06, 1.18)

Table 19: Percent change in the duration of hospitalization and total charges for patients with CDI according to region with West as the reference *adjusted for hospital teaching status*

Region (adjusted)	All patients with CDI (95% CI)		1° CDI (95% CI)		2° CDI (95% CI)	
Hospital Duration	West	Reference	West	Reference	West	Reference
	South	4% (1%, 7%)	South	12% (9%, 14%)	South	3% (1%, 7%)
	Midwest	-16% (-18%, -14%)	Midwest	-4% (-6%, -2%)	Midwest	-16% (-19, -14%)
	Northeast	10% (6%, 13%)	Northeast	13% (10%, 16%)	Northeast	9% (5%, 13%)
Total Charges	West	Reference	West	Reference	West	Reference
	South	5% (-11%, 24%)	South	14% (-2%, 32%)	South	9% (-7%, 28%)
	Midwest	-30% (-43%, -14%)	Midwest	-22% (-35%, -7%)	Midwest	-30% (-43%, -14%)
	Northeast	52% (19%, 94%)	Northeast	42% (17%, 71%)	Northeast	43% (11%, 83%)

Table 20: Odds ratios for having a CDI diagnosis and for dying with CDI according to region *with Northeast as the reference*

Region	All patients with CDI (95% CI)		1° CDI (95% CI)		2° CDI (95% CI)	
Odds of CDI	Northeast	Reference	Northeast	Reference	Northeast	Reference
	Midwest	0.86 (0.80, 0.91)	Midwest	0.98 (0.91, 1.06)	Midwest	0.79 (0.74, 0.86)
	South	0.84 (0.79, 0.89)	South	0.91 (0.85, 0.97)	South	0.79 (0.74, 0.85)
	West	0.83 (0.78, 0.89)	West	0.82 (0.75, 0.88)	West	0.84 (0.78, 0.92)
Case fatality	Northeast	Reference	Northeast	Reference	Northeast	Reference
	Midwest	0.67 (0.64, 0.71)	Midwest	0.73 (0.67, 0.79)	Midwest	0.68 (0.64, 0.71)
	South	0.81 (0.77, 0.85)	South	0.77 (0.71, 0.84)	South	0.83 (0.80, 0.87)
	West	0.88 (0.83, 0.92)	West	0.71 (0.64, 0.78)	West	0.89 (0.84, 0.93)

Table 21: Percent change in the duration of hospitalization and total charges for patients with CDI according to region with *Northeast as the reference*

Region	All patients with CDI (95% CI)		1° CDI (95% CI)		2° CDI (95% CI)	
Hospital Duration	Northeast	Reference	Northeast	Reference	Northeast	Reference
	Midwest	-24% (-26%, -22%)	Midwest	-15% (-17%, -14%)	Midwest	-24% (-26%, -21%)
	South	-5% (-8%, -3%)	South	-2% (-4%, 0%)	South	-6% (-8%, -3%)
	West	-9% (-12%, -6%)	West	-12% (-14%, -10%)	West	-9% (-12%, -6%)
Total Charges	Northeast	Reference	Northeast	Reference	Northeast	Reference
	Midwest	-52% (-55%, -49%)	Midwest	-48% (-51%, -44%)	Midwest	-50% (-54%, -46%)
	South	-30% (-35%, -25%)	South	-24% (-29%, -18%)	South	-26% (-32%, -19%)
	West	-46% (-51%, -41%)	West	-42% (-47%, -36%)	West	-49% (-55%, -44%)

DISCUSSION

Recent epidemiologic studies have found considerable variability in the incidence rates of CDI in different regions of the United States and among hospitals with different characteristics.[3,17] However, these studies did not adjust for the patient-level risk factors for CDI, including age, chronic comorbidities, and exposure to antibiotics, corticosteroids, and proton pump inhibitors[10,18-25] Therefore, these analyses may be potentially flawed by failing to adjust for the patient case mix. In our study, we adjusted for a number of patient-level characteristics and demonstrated that significant differences persisted in 1) CDI rates of occurrence, 2) in-hospital case fatality rates among CDI patients, 3) duration of hospitalization among CDI patients, and 4) amount of hospital charges for CDI patients at different types of hospitals.

Moreover, we found the incidence rates of CDI increased steadily each year (55 cases in 2003 to 99 cases in 2012 per 100,000 population), which is similar to other epidemiological studies that have estimated the risk of health care-associated CDI to be between 60 to 93 cases per 100,000 patients.[4,26,27] Our study also reflects rates that show an increasing incidence of community-acquired CDI (130 cases per 100,000 patients in 2003 to 330 cases per 100,000 in 2012) although these rates are lower than have been found in other studies. This may be due to discrepancies in coding or a limitation of our ICD-9 definition for determining primary and secondary CDI.[18,27]

We found that urban and teaching hospitals were associated with higher odds than rural and nonteaching hospitals, respectively, of having patients with CDI and dying in the hospital from CDI or secondary CDI. Urban and teaching hospitals were also associated with a longer duration of hospitalization and higher charges per hospitalization. One reason may be that urban, teaching hospitals are more likely to offer specialized services, such as transplant programs and burn center services, which previous studies have shown to be associated with an increased burden of CDI.[3,28-30]

Our regional analysis of CDI showed that being hospitalized in the Northeast was associated with higher CDI rates, in-hospital death rates, increases in duration of hospitalization and amount of hospital charges even when adjusting for hospital teaching status. Other studies have shown similar regional variability, with one showing that CDI was more prevalent in Emergency Rooms in the Northeast.[31] One theory is that these regional differences may be driven by spread of the highly virulent BI/NAP1/027 strain, which has 15 times more the toxigenicity of other *C. difficile* strains and has caused outbreaks in Pittsburgh, Pennsylvania, and Quebec, Canada.[5,6,32] An epidemiological study on *C. difficile* strain isolates showed that the Northeast had the highest prevalence of BI/NAP1/027, while the West, the region with the lowest incidence of CDI in our study, has had decreasing prevalence of this *C. difficile* ribotype.[33]

In our study, primary CDI rates and outcomes were also significantly worse in the Northeast compared with other regions of the country, which suggested that the Northeast has a high burden of CDI in the community as well as in healthcare settings. This further

supports the BI/NAP1/027 strain's potential role in CDI regional variability, as this strain has been shown to be prevalent in both the community and in hospital settings.[34,35] Still, the marked regional differences we found in our study cannot be fully explained by the prevalence of this strain alone. While we did find an increased odds of dying with CDI in the Northeast, other studies have found no differences in poor CDI outcomes, including case fatality, with infections of this strain in general.[36] More studies are needed to determine if other regional factors may be attributing to this discrepancy.

There was no significant association between the hospital bed size and the odds of acquiring CDI. However, the largest hospitals were associated with higher odds of dying with CDI as well as a longer duration of hospitalization and a higher amount of total charges for patients with any CDI diagnosis. When analyzing for the number of discharges, an increase in 1,000 discharges accounted for increases in the odds for a patient having a CDI or secondary CDI diagnosis or dying with that diagnosis. Hospitals with more discharges were also associated with a longer average duration of hospitalization and total charges. These findings are in contrast with the results of a previous study that determined characteristics of hospitals with a high CDI burden, showing that these "high CDI burden" hospitals had fewer beds and lower bed turnover (fewer discharges per bed) than "low CDI burden" hospitals.[3] However, that study was limited to three states, none of which was found in the Northeast, the region with the highest burden of CDI, while our study was done on a national sample. Other studies supportive of our findings include one study showing that larger hospitals (by square feet) were associated with increased CDI and another study based on the National

Nosocomial Infection Surveillance System finding that CDI rates increased significantly from 1987 to 2001 in intensive care units in hospitals with greater than 500 beds.[17,37]

We also investigated the association between multi-hospital membership status and classification and CDI rates and outcomes. Previous studies, though not done on patients with infections, have shown that admission to hospitals that are members of a multi-hospital system have better outcomes, including lower case fatality rates, which may be partly due to better service offerings and better coordination of care.[38] The association between multi-hospital membership and CDI rates has not previously been investigated. In our study, we found that members of a multi-hospital system were not associated with higher odds of CDI acquisition or CDI case fatality, but were associated with a longer duration of hospitalization than hospitals that were not part of a multi-hospital system. Across hospital system classifications, we found that independent hospitals had significantly higher CDI or secondary CDI acquisition odds and significantly higher case fatality odds for all CDI, primary CDI, and secondary CDI. More studies are needed to determine the association between multi-hospital system membership and other nosocomial infections.

In this study, we also investigated the association between nursing FTE's and CDI rates and outcomes. We found that hospitals with a higher percentage of RNs were associated with a decreased average duration of hospitalization among patients with CDI, primary CDI, or secondary CDI. Also, we found that increases in LPN FTE were associated with more hospital charges for patients with CDI and a longer duration of hospitalization for

patients with primary CDI, but had no significant association with the odds of CDI acquisition or CDI-related death. Previous studies have shown that a high RN to patient ratio is associated with increased rates of hospital acquired infections, increased in-hospital case fatality for all causes, and hospitalization cost.[39,40] These were thought to be due to increased burnout and job dissatisfaction among nurses which led to, for example, a higher nurse turnover and less experienced nurses.[39-41] Hospitals with a higher percentage of RNs among all nursing staff have also been previously shown to be associated with lower 30-day all-cause case fatality rates.[42] However, no previous studies have focused on the relationship between the number of nurses and CDI. Future studies are needed to determine if a higher ratio of RN to RN FTE, which would imply more nurse turnover and a higher nurse to patient ratio, is associated with differences in CDI incidence and CDI outcomes.

Study strengths and limitations:

To the best of our knowledge, this study is the largest national analysis of CDI rates, in-hospital case fatality, duration of hospitalization, and total hospitalization charges. Also, to our knowledge, it is the first CDI-related study to use hierarchical modeling to account for hospital-level clustering of patients. Finally, it is the first study on hospital-level CDI risk factors that adjusted for patient-level characteristics.

Nonetheless, this study also had several limitations. First, NIS consists of discharge level data. For example, if a patient had two subsequent admissions for the same CDI episode,

this analysis would have considered those admissions as two different patients. Second, ascertainment bias may have been introduced as the case definition of CDI is by ICD-9-CM coding rather than toxin identification, which is not included in the database. However, previous studies have noted that using ICD-9-CM for CDI has a 70% sensitivity with nearly 100% specificity as compared with diagnosing CDI by toxin identification.[43] Variations in the diagnostic method for CDI detection (antigen detection, enzyme immune-assay, or polymerase chain reaction) were not accounted for. Furthermore, the database does not have variables for the main risk factor for CDI, which is prior antibiotic use. Finally, different years of the database included different states (with more states added each year). Therefore, there was year-to-year heterogeneity although this was minimized by using hierarchical modeling as well as adjusting for the year of admission.

Conclusions:

Our study showed that after adjusting for patient associated characteristics, considerable clinical and statistical variation for hospitals for CDI rates and outcomes persisted. More studies are needed to determine the impact of any interaction between hospital-level characteristics. Our results indicate the importance of accounting for both patient-level and hospital-level characteristics in future CDI related epidemiological investigations.

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