2010

When Volunteering Doesn't Cut It: A critical examination of Carbapenem-Resistant Enterobacteriaceae Surveillance and Trends in the United States.

Erica E. Smith
Virginia Commonwealth University

Master of Public Health Research Project

When Volunteering Doesn't Cut It: A critical examination of Carbapenem-Resistant Enterobacteriaceae Surveillance and Trends in the United States.

by
Erica E. Smith

MPH Advisor: Amy Pakyz, PharmD

MPH Research Project Advisor: Kate L. Lapane, PhD

Department of Epidemiology and Community Health
Master of Public Health Program
MPH Research Project: EPID 691

Virginia Commonwealth University
Richmond, Virginia

May, 2010

ABSTRACT

Background. Carbapenem-resistant Enterobacteriaceae, including *Escherichia coli* and *Klebsiella pneumoniae*, are newly emerging pathogens of public health importance. Currently no nationally representative or mandatory surveillance or reporting system exists to examine trends of these important pathogens.

Objective. The purpose of the current study was to estimate trends in overall microbial burden and carbapenem resistance in *E. coli* and *K. pneumoniae* and to understand the extent to which hospitals which report to voluntary surveillance systems represent all hospitals in the United States.

Design. We conducted a descriptive study to compare the hospitals participating in voluntary reporting systems of the University HealthSystem Consortium and the National Healthcare Safety Network with the Healthcare Utilization Project's Nationwide Inpatient Sample, a nationally representative sample of hospital discharges.

Methods. Descriptive analyses examined hospital characteristics (region, bed size, hospital control, teaching status, case mix index) and patient characteristics (age, sex, race/ethnicity, admission source, admission type, discharge status, primary payer) of participant hospitals versus all US hospitals. ICD-9-CM codes identified discharges coded for *E. coli* and *K. pneumoniae* diagnoses; linear regression was used to evaluate trends in overall microbial burden of *E. coli* and *K. pneumoniae* in all US Hospitals and US Academic Centers. Trends in *E. coli* and *K. pneumoniae* resistance to carbapenem were also evaluated in hospitals participating in voluntary surveillance systems (n=13).

Results. Between 2002 and 2007, slight increasing trends in burden of both *E. coli* and *K. pneumoniae* were observed (*E. coli*: slope = 0.0537; *K. pneumoniae* slope = 0.0168). Hospitals participating in voluntary surveillance systems are larger and care for fewer elderly patients than all US hospitals.

Conclusions. These results suggest that hospitals that participate in voluntary surveillance systems like the National Healthcare Safety Network and the University HealthSystem Consortium may underrepresent trends in smaller hospitals, as well as those that treat elderly patients. Increasing overall burden of infection due to these isolates only reinforces the importance carbapenem resistance in *E. coli* and *K. pneumoniae*. This important public health threat may warrant the creation of a national, mandatory reporting system for these and other antimicrobial resistant organisms.

INTRODUCTION

Antimicrobial resistance, especially in heath care settings, has emerged as a significant public health threat.[1] As multidrug resistant organisms have increased, so has use of broad spectrum agents to treat them.[1] With their broad spectrum activity for gram positives, gram negatives and anaerobic bacteria,[2] carbapenems are frequently used as a last line of therapy.[3,4]

Newer antimicrobial resistant species such as Carbapenem-resistant Enterobacteriaceae (CRE), including *Escherichia coli* and *Klebsiella pneumoniae* are beginning to emerge. Enterobacteriaceae are gram-negative bacteria which are part of the normal human intestinal flora and are frequently spread via fecal-oral contamination.[1] Pathogenic isolates can be carried in the gut for years in healthy adults and only emerge when intestinal conditions change.[1]

The first carbapenem resistance was seen in *K. pneumoniae* in 2000 in a hospital in New York city;[5] the first carbapenem hydrolyzing enzymes in *E. coli* isolates were found in 2005.[6] Most alarming was the discovery of a community-associated isolate of carbapenem-resistant *E. coli* in Greece in 2009.[7] CRE was originally identified in the Northeast United States,[5] but are now beginning to spread in the United States and Europe.[8]

The emergence of CRE is a great public health concern because there is no reliable treatment. CRE are typically resistant not only to carbapenems, but also to polymixin B sulfate and third generation cephalosporins.[5] In addition, many carbapenem resistant isolates of *K. pneumoniae* also possess extended spectrum beta-lactamases,[5] and genes conferring resistance may be accompanied by virulence factors.[1] In many cases, *in vitro* analysis has shown some isolates to be susceptible to tigecycline, gentamicin, and colistin.[5,9-11] Clinical treatment successes have resulted from combinations of gentamicin and colistin[12] or tigecycline and colistin.[13] In a case control study, removal of infection site was also part of a successful

treatment strategy.[14] With few novel treatment options in development, treatment of CRE infections remains challenging.

Despite the severity of the emerging CRE and other multi-drug resistant organisms, the US currently has only voluntary antimicrobial resistance surveillance systems. Due to their low incidence in any single institution, it is likely that current, voluntary public health surveillance systems underrepresent the spread of these organisms.[1] One surveillance system currently in use is the National Healthcare Safety Network. Designed to be a national surveillance system for both patient and healthcare personnel safety, it began collecting data from participant hospitals in 2005.[15] Another example is the University HealthSystem Consortium which, represents approximately 90% of the United States' non-profit academic medical centers,[16] and through collaboration among participant hospitals, has provided a limited mechanism of surveillance of data from its member organizations since 2002. No single mandatory reporting system exists to track the emergence and increase of these dangerous pathogens. The purpose of this study was twofold. First, we estimated trends in both overall microbial burden and carbapenem resistance in *E. coli* and *K. pneumoniae*. Second, we sought to understand the extent to which hospitals pzrticipating in voluntary surveillance systems represent all hospitals in the United States.

METHODS

We conducted a descriptive study to evaluate the extent to which voluntary public health reporting surveillance systems of carbapenem-resistant Enterobacteriaceae (CRE) may adequately represent all hospitals in the US. This study was not funded and the authors have no conflicts of interest to disclose.

Data Sources

Between September 2009 and January 2010, we thoroughly investigated multi-site data sources of antimicrobial resistance and identified two: the National Healthcare Safety Network (NHSN) and the University HealthSystem Consortium (UHC). We also identified two data sources which provide nationally representative hospital estimates: the National Hospital Discharge Survey and the Healthcare Utilization Project Nationwide Inpatient Sample (HCUP-NIS). While the latter data sources both enable nationally representative estimates of hospital discharges, we selected the HCUP-NIS for three reasons. First, its larger sample size and greater number of available diagnosis codes enabled estimation of rare events (such as CRE) with greater precision. Second, this source provided a more extensive array of data elements important for this research. Third, the HCUP-NIS provided data specifically on hospital characteristics, which allowed stratification by teaching status. Each data source used in final analysis is discussed in detail below.

The University HealthSystem Consortium (UHC)

The University HealthSystem Consortium (UHC) is composed of 107 participant academic medical centers and 233 of their associated hospitals, representing approximately 90% of the United States' non-profit academic medical centers.[16] The UHC provides a mechanism for collaboration for research across academic medical centers, which are geographically distributed throughout the US.[16] Approximately 75 academic medical centers participating in the UHC Clinical Database/Resource Manager module were approached by investigators at VCU for participation in surveillance of microbial-resistance rates. Investigators requested antibiograms from each hospital for each year from 2002 to 2008. Hospitals were provided with a $100 incentive per year for sharing their data. Isolates were categorized as either susceptible or resistant; each hospital used their own standards to measure antimicrobial sensitivity (not reported). Hospitals were considered "UHC Participant Hospitals" and included in descriptive

distribution analysis if they contributed antibiogram data for at least one year in the study period (2002-2008, n=42). Hospitals were included in descriptive trend analysis only if data were available for all years in the study period (2002-2008, n = 13).

National Healthcare Safety Network (NHSN)

Data from the National Healthcare Safety Network (NHSN) are not available publicly. While we were unable to secure data from the NHSN, we were able to extract data from a published report based on the NHSN.[15] The NHSN was implemented in 2005, integrating three former systems: the National Nosocomial Infections Surveillance (NNIS) system, the Dialysis Surveillance Network and the National Surveillance System for Healthcare Workers. Managed by the Centers for Disease Control and Prevention Division of Healthcare Quality Promotion, the NHSN compiles monthly electronically reported surveillance data on healthcare associated infections in approximately 460 participant healthcare facilities.[15]

Healthcare Cost and Utilization Project- Nationwide Inpatient Sample (HCUP-NIS)

The Nationwide Inpatient Sample (NIS) is part of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality. HCUP-NIS data are collected to track and analyze national trends in health care utilization, access, charges, quality and outcomes.[17]

The HCUP-NIS uses about 1,000 hospitals to draw a nationally representative, complex sample of US non-federal, short-term, general, specialty and non-institutional community hospitals. From each sampled hospital, all discharges for the sample year are included, totaling 5 to 9 million annual discharges, enabling analyses of rare conditions such as *E. coli* and *K. pneumoniae*. Available data contain both hospital and patients characteristics; the number of included diagnosis codes per discharge varies over time and by state.[17,18]

ANALYSIS

Evaluation of the National Burden of Total *Escherichia coli* and *Klebsiella pneumoniae* Diagnoses

We evaluated trends in the national burden of *Escherichia coli* and *Klebsiella pneumoniae* infections from all US Hospitals and US Academic Centers. Hospital discharge data from the HCUP-NIS were used to measure the total national burden of *E. coli* and *K. pneumoniae* diagnoses (regardless of antibiotic susceptibility). As the number of ICD-9-CM codes captured in the HCUP-NIS varies over time and by state, up to 15 International Classification of Disease (ICD)-9-CM codes were captured for each discharge record. All infection diagnosis codes of either infection (*E. coli:* 008.0, 008.00, 008.01, 008.02, 008.03, 008.04, 008.09, 038.42, 041.4, 482.82; *K. pneumoniae*: 482.0, 041.3) were aggregated separately by year. Thus for each year, the proportion of hospital discharges with a diagnosis of *E. coli* or *K. pneumoniae* was calculated for 2002-2007, the most recently available data.

From these aggregated data, we developed two linear regression models; one using the dependent variable for presence of any ICD-9-CM code for *E. coli*, and one for *K. pneumoniae*. Each model included a single determinant- year. We interpreted the beta coefficient for the determinant as the change in proportion of diagnoses of *E. coli* (or *K. pneumoniae*) per one unit increase in year.

Carbapenem Resistance Trends among Select UHC Participant Hospitals

Using antibiogram data available from the UHC Participant Hospitals, we conducted a descriptive evaluation of CRE resistance trends. Aggregate incident annual sensitivity data on carbapenem resistant isolates of *Klebsiella pneumoniae* and *Escherichia coli* were extracted from available antibiograms for analysis. Carbapenem resistance was normalized per 1,000 discharges annually for each species. As there were only 13 hospitals contributing data for all years, no

statistical tests were completed; data were plotted to visually inspect for descriptive trends in resistance.

Comparison of Patient and Hospital Characteristics

To assess the extent to which hospitals participating in non-mandatory surveillance of CRE are similar to all hospitals nationwide, and whether discharges from these participant hospitals are similar to those from hospitals nationwide, we first examined which conceptual domains were available for analysis across both HCUP-NIS and UHC data sources. Once identified, we compared aggregated discharge-level and hospital-level characteristics. To better approximate the population of academic medical centers from which UHC hospitals are selected, stratified analysis using hospitals from the HCUP-NIS was completed using two samples: 1) All US Hospitals: All hospitals sampled by the HCUP-NIS and 2) US Academic Centers: HCUP-NIS Academic Medical Centers, limited to self-identified teaching hospitals.

The comparisons of interest were 1) all US Hospitals versus UHC Participant Hospitals; and 2) US Academic Centers versus UHC Participant Hospitals. For analysis of HCUP-NIS data, we weighted for complex survey design using appropriate SAS survey procedures. P-values based on large samples such as this one are rarely of use because unimportant differences will be statistically significant.[19] Therefore, we *a priori* used an absolute difference of 5% in distributions to indicate evidence of meaningful differences.

Discharge-level characteristics included: patient age group (younger than 18; 18-30 years; 31-50 years; 51-64 years; 65 and older), gender, race/ethnicity, (White; Black/African American; Hispanic/Latino; Asian/Pacific Islander; American Indian/Alaskan Native), admission source (emergency room; another hospital; another facility; court/law enforcement; routine, birth or other), admission type (emergency; urgent care; elective; newborn; trauma center), discharge

status (died or did not die during hospitalization), and primary payer source (Medicare; Medicaid; private insurance or HMO; self pay; no charge for provided service; other).

Hospital-level variables included: geographic region, teaching status, bed size, hospital control, and mean case mix index. Region was defined using four regions (Northeast, Midwest, South, West), as characterized by the US Census Bureau. Hospital teaching status was self-designated by each facility as teaching or non-teaching. For HCUP-NIS data, bed size was categorized as "small" "medium" or "large", and was based on the number of hospital beds specific to the individual hospital's region, location and teaching status, as described previously.[17] To approximate this distribution, UHC hospital bed sizes were divided similarly to teaching centers captured by the HCUP-NIS: small, (< 250 beds) medium (250-399 beds) and large (> 400 beds). NHSN bed size analysis was extracted from an available report[15] and was categorized as small, (< 200 beds) medium, (200 - 499 beds) and large (> 500 beds).

For the HCUP-NIS, when the sample size of hospitals was sufficiently large, hospital control was stratified as "public", "non-profit", and "proprietary." For smaller strata, stratification was simply "public" and "private, collapsed." For all other strata, no stratification was done due to small sample size, all hospitals were categorized as "collapsed, no control stratification done," as described previously.[20]

Hospital case mix index (CMI) was calculated using diagnosis related group (DRG) relative weights downloaded from the Centers for Medicare and Medicaid Services.[21] DRG weights were applied to each discharge based on reported DRG and then hospital CMI was calculated as described previously.[22] CMI for each hospital from the HCUP-NIS were averaged, resulting in a mean CMI across all US Hospitals and US Academic Centers (assessed separately). For UHC Participant Hospitals, CMI was provided for each hospital, and a mean CMI measure was calculated.

RESULTS

Evaluation of the National Burden of *Escherichia coli* and *Klebsiella pneumoniae*

Figure 1 shows the proportion of hospital discharges with a diagnosis of *E. coli* (Panel A) and *K. pneumoniae* (Panel B) for all US Hospitals and US Academic Centers. Between 2002 and 2007, increases in the proportion of discharges for both *E. coli* and *K. pneumoniae* were observed. In 2007, an estimated 149,767 hospital discharges included codes for *E. coli* and 562,809 for *K. pneumoniae* (among all US Hospitals). In both cases, higher *E. coli* and *K. pneumoniae* diagnosis rates were seen at US Academic Centers than at all US Hospitals. For all discharges from US Hospitals with a diagnosis of *E. coli* or *K. pneumoniae*, evidence of slight positive linear trends were shown for both species (*E. coli*: slope = 0.0537, Std. Err. = 0.00547; *K. pneumoniae* slope = 0.0168, Std. Err. = 0.00197). For discharges from US Academic Centers, evidence of positive linear trends were also shown for both species (*E. coli*: slope =0.0489, Std. Err. = 0.00580; *K. pneumoniae* slope = 0.01993, Std. Err. = 0.00113).

CRE Antibiogram Trends among UHC Participant Hospitals

Figure 2 shows the trends in aggregate carbapenem resistance of *Klebsiella pneumoniae* and *Escherichia coli.* For carbapenem resistance in *E. coli*, no clear directional trend was seen, other than a nominal decrease in resistance in 2005. Hospital-level resistance rates in this species seem to be stable for the years evaluated. For *K. pneumoniae*, the data point toward evidence of a slight decrease in resistance until 2005, at which point an increasing trend begins to emerge. Current rates are nominally higher than those found earlier in this decade (data not shown).

Comparison of Patient Characteristics

Table 1 shows the comparison of discharges from hospitals which participate in voluntary surveillance systems of CRE to discharges from all US hospitals, as well as all US Academic Centers. Overall, characteristic distributions of discharges from UHC Participant Hospitals approximated all US Academic Hospitals. There were meaningful differences between hospitals

voluntarily reporting CRE surveillance data and all US hospitals with respect to patient age, race/ethnicity, admission source and primary payer source.

More discharges from all US hospitals were from patients 65 or older (US Hospitals: 33.5%, US Academic Centers: 29.1% and UHC Participants: 24.3%) and had Medicare as their primary payer source (US Hospitals: 36.4%, US Academic Centers: 31.9%, and UHC Participants: 29.5%). With respect to reported race/ethnicity, discharges from all US Hospitals were more frequently White (US Hospitals: 67%, US Academic Centers: 59.6% and UHC Participants: 60.7%), while discharges from UHC Participant Hospitals were more frequently Black/African American (US Hospitals: 15%, US Academic Centers: 19.2%, UHC Participants: 24.7%).

Differences were also observed for admission source: discharges from all US Hospitals were more likely admitted from the emergency room, (US Hospitals: 44.5%, US Academic Centers: 42.8%, and UHC Participants: 39.4%) while those from UHC Participant Hospitals were more likely admitted from another hospital (US Hospitals: 3.3%, US Academic Centers: 4.6%, UHC Participants: 7.9%).

Comparison of Hospital Characteristics

Table 2 shows the comparisons of hospital characteristics: hospitals who voluntarily report CRE surveillance rates to all US Hospitals and US Academic Centers. UHC Participant Hospitals were better approximated by US Academic Centers than by all US Hospitals. Relative to all US hospitals, the UHC Participant Hospitals overrepresented the Northeast, underrepresented the Midwest and Southwest. UHC Participant Hospitals underrepresented small hospitals overall, as well as small academic hospitals (US hospitals: 45.2%, US Academic Centers: 28.0%, UHC Participants: 4.8%). When comparing UHC Participant Hospitals to NHSN Participant Hospitals, UHC Hospitals were more likely to be large (UHC: 73.8%, NHSN:

20.5%). All UHC Participants Hospitals were non-profit teaching centers. While only 18.2% of all US Hospitals are teaching centers, because of UHC's deliberate sampling on academic medical centers, 100% of their hospitals are teaching centers. UHC Participant Hospitals also had a higher mean case mix index (CMI = 1.64, Std. Dev. = 0.18) compared to all US Hospitals (CMI = 1.18, Std. Dev. = 0.0005) and US Academic Centers (CMI = 1.25, Std. Dev. = 0.0009).

DISCUSSION

Overall, we observed slight increased trends in hospital discharges coded *E. coli* and *K. pneumoniae* diagnoses. No distinct trend in carbapenem resistance in *E. coli* was observed in the 13 hospitals with consistent contributions to the voluntary reporting system, but suggestions of an increase in carbapenem resistance in *K. pneumoniae* since 2005 is apparent. We found that hospitals participating in volunteer CRE surveillance systems may not adequately represent all US hospitals. Hospitals participating in voluntary reporting systems underrepresent hospitals in the South and Midwest US. Further, the hospitals voluntarily reporting are likely not capturing trends or resistance in small hospitals, as well as proprietary or public hospitals. While discharge patient characteristics of hospitals participating in voluntary reporting systems for CRE better approximate US Academic Centers than by all US Hospitals, the participating hospitals tend to underrepresent patients aged 65 and older and Medicare recipients. Conversely, UHC Participant Hospitals also over-represent people who were Black/African American. Discharges from UHC Participant Hospitals were more frequently admitted from other hospitals.

Larger hospitals more frequently participate in studies of organizational and procedural determinants of infection and control and patient safety programs,[23-25] though results presented here indicate that smaller hospitals actually make up the plurality of all US Hospitals. Larger, teaching, urban hospitals may have a better quality of care than non-teaching, small, rural

hospitals.[26] For-profit hospitals may have higher mortality rates than public or non-profit hospitals, and private teaching hospitals have lower mortality rates than private non-teaching hospitals.[27] Larger hospitals and teaching hospitals have higher rates of several antimicrobial resistant organisms.[28] Larger hospitals are also more likely to have staff infection control specialists and/or laboratory personnel[23] who may more easily facilitate surveillance and reporting internally and externally. Teaching hospitals are also more likely to have an accurate, disseminated and up-to-date antibiogram,[24] typically used empirically to aid in clinical decision making. For-profit hospitals tend to detect and internally report antimicrobial resistance less frequently than other hospitals.[24] Importantly, evidence suggests that antimicrobial monitoring and control systems at individual institutions are more frequently implemented as a reaction to high resistance rates, rather than proactively for prevention.[24] As such, interpreting findings from hospitals participating in voluntary surveillance systems may not adequately capture emerging trends in resistance.

While increasing age is predictive of CRE infection, gender was not found to be predictive;[3] these and other demographic factors, like race/ethnicity, warrant further investigation. Typically, independent predictors of CRE infection comprise use of antibiotics,[3] including carbapenems,[3,10,29] and cephalosporins;[4,29] aminoglycosides have previously been shown as protective.[4] Conflicting evidence in the literature exists over the importance of fluoroquinolones as predictive[3,4,10] or protective[29]. Poor functional status and illness severity have also been shown to be predictive,[3,4] while presence of comorbid conditions was not associated.[4] Stay in the intensive care unit (ICU) has also been predictive of resistant *K. pneumoniae* isolation in some studies,[3,10] while conflicting evidence is indicated in another.[29]

While overall the proportions of discharges coded with diagnoses of *E. coli* or *K. pneumoniae* are small (~1%), our study indicated evidence of slight increasing trends in both *E.*

coli and *K. pneumoniae*, coupled with the rise in resistance in *K. pneumoniae.* If overall burden is increasing, so is to the opportunity for resistance. Without proper, mandatory reporting and surveillance measures for these important public health pathogens, it is impossible to monitor true nationwide prevalence in CRE bacteria. Although current mandatory monitoring of "traditional" communicable disease by state health departments and the Centers for Disease Control and Prevention is far from perfect, these systems provide mechanisms of surveillance and evaluation to drive program planning at all levels of government, and are especially effective when electronic reporting is used.[30,31] For a program mandating reporting of health-care associated infections to come to fruition, it is imperative that this issue become both an ideological and fiscal priority.

Proper surveillance of national trends may spur diffusion of promising prevention and infection control efforts. In a New York hospital where CRE infections are becoming endemic in the ICU, a comprehensive intervention including cohorting of specific patient groups, routine rectal surveillance, increased contact isolation and hand hygiene vigilance, and decontamination of the environment was successful in mitigating an outbreak of CRE.[11] Improvements in hand hygiene, contact precautions and antimicrobial use have also been suggested as prevention mechanisms for CRE infections.[32] These and other mechanisms of prevention will no doubt save time, finances and lives if CRE and other antimicrobial resistant infections can be prevented.

This study must be considered with certain caveats. First, we were only able to evaluate antibiogram resistance in a very small sample and each hospital used independent testing methods (not reported). Resistance in CRE can be measured in one of several ways, including antibiotic sensitivity analysis,[12,33] the Hodge test or modified versions,[33] or PCR,[33,34] Nevertheless, all methods are imperfect at detecting CRE *in vitro*,[5,33] especially typical and routine automated methods.[5,35]. Second, the extent to which we were able to explore hospital and

patient characteristics was a function of the data elements available. Yet, we were able to provide a comparison of relatively small reporting systems with a large, nationally representative sample of patient discharges and hospital characteristics which provides accurate estimates of US hospitals. The HCUP-NIS is well suited for examining rare diagnoses like *E. coli* and *K. pneumoniae* and allowed us to stratify hospitals by teaching status. Lastly, the number of ICD-9-CM codes reported to HCUP varied through time and place. Although we analyzed trend data according to HCUP standards, it may be that increasing trends were a function of increases in the number of diagnoses reported rather than true increases in burden.

CONCLUSIONS

Antimicrobial resistance has emerged as a significant public health threat, with the past quarter-century "ushering in the era of multidrug resistance."[1] Carbapenem resistance is newly emerging in isolates like *Escherichia coli* and *Klebsiella pneumoniae*. Increasing overall burden of infection due to these isolates only reinforces CRE as an important public health threat and may warrant the creation of a national, mandatory reporting system for these and other antimicrobial resistant organisms. Due to the current climate of pharmaceutical production, preventing the further creation and spread of drug-resistant isolates will not likely stem from new therapeutics, but rather from control, isolation and antimicrobial stewardship practices across healthcare settings.[32]

Figure 1. The National Burden of *Escherichia coli* and *Klebsiella pneumoniae*

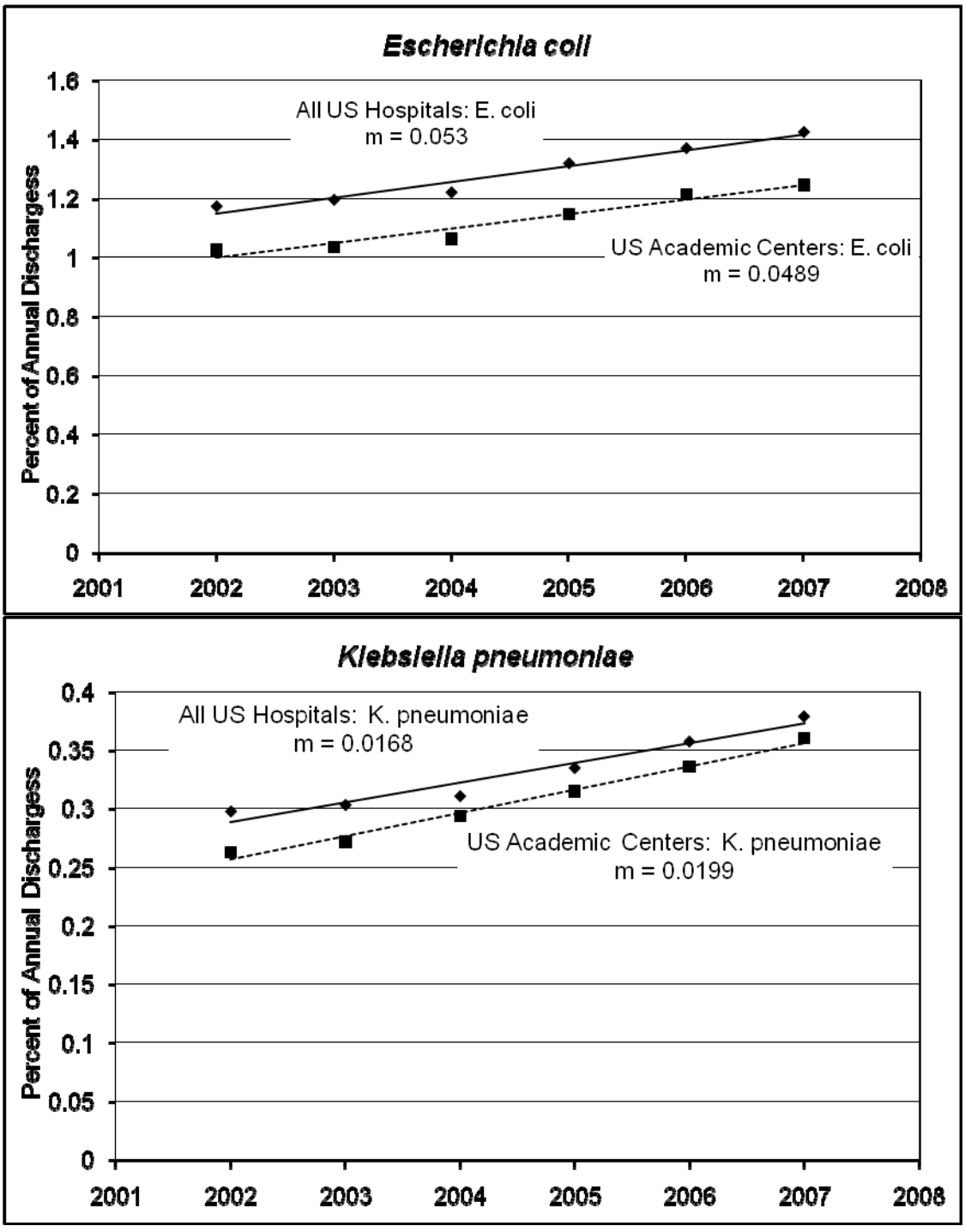
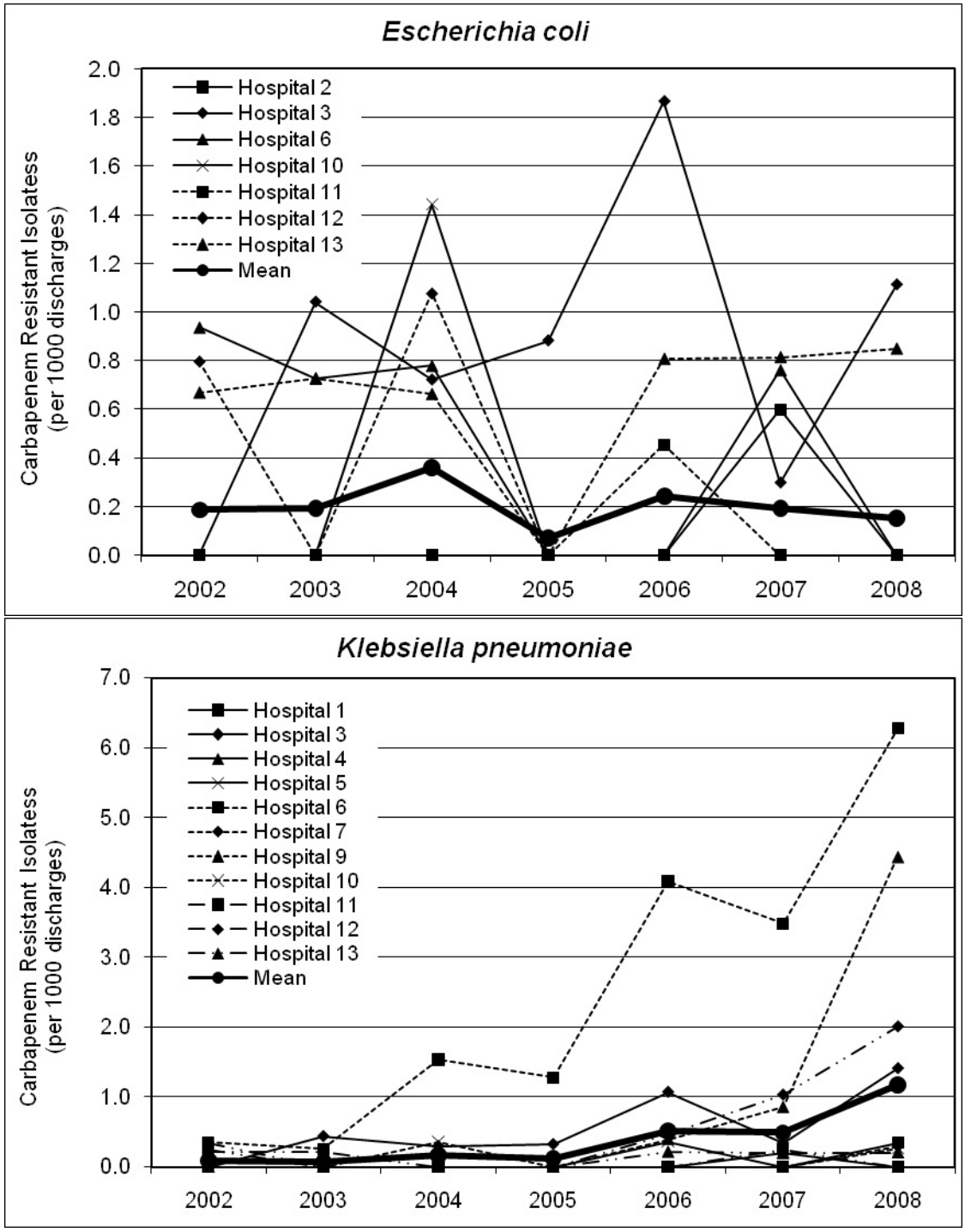


Figure 2. Carbapenem Resistance Trends in *Escherichia coli* and *Klebsiella pneumoniae*- select* UHC Participant Hospitals (n=13)



*There were 13 UHC Participant Hospitals for which data were available for all years; Means reflect all 13 hospitals. Individual hospitals were not graphed here if data for all years reflected no resistance (0.000).

Table 1: Patient Level Variables, 2007 Discharges

	US Hospitals	US Academic Centers	UHC Participant Hospitals
Sample Size	8,043,415	3,758,898	1,268,496
Weighted Sample Size	39,541,948	18,760,902	N/A
	Weighted Percentage	Weighted Percentage	Percentage
Patient Age			
Younger than 18 years	17.2	19.2	16.2
18 to 30 years	12.9	13.3	14.4
31 to 50 years	19.7	21.0	24.0
51 to 64 years	16.8	17.4	21.1
65 and older	33.5	29.1	24.3
Patient Sex			
Female	58.8	57.6	54.4
Patient Race/Ethnicity			
White	67.0	59.6	60.7
Black or African American	15.0	19.2	24.7
Hispanic or Latino	14.2	16.4	11.5
Asian or Pacific Islander	0.9	1.1	2.5
Am. Indian/Alaskan Native	2.9	3.6	0.5
Admission Source			
Emergency Room	44.5	42.8	39.4
Another Hospital	3.3	4.6	7.9
Another Facility	1.3	1.2	1.5
Court/Law enforcement	0.1	0.1	0.1
Routine, Birth or Other	50.7	51.2	50.4
Admission Type			
Emergency	45.7	45.6	41.3
Urgent Care	17.9	16.2	19.3
Elective	25.0	26.2	28.1
Newborn	11.2	11.6	9.2
Trauma Center	0.2	0.4	1.3
Discharge Status			
Died during hospitalization	1.9	1.9	2.2
Primary Payer Source			
Medicare	36.4	31.9	29.5
Medicaid	19.4	21.3	22.1
Private Insurance	34.8	36.4	36.7
Self Pay	5.3	5.6	5.4
No Charge for Service	0.5	0.7	0.0
Other	3.5	4.0	5.5

Table 2: Hospital Level Variables, 2007

	US Hospitals	US Academic Centers	UHC Participant Hospitals	NHSN Participant Hospitals
Sample Size	1,044	191	42	462
Wt. Sample Size	5,099	927	N/A	N/A
	Weighted Percentage	Weighted Percentage	Percentage	Percentage
Region				
Northeast	12.8	24.4	26.2	
Midwest	29.2	27.3	21.4	
South	39.9	31.0	31.0	
West	18.2	17.2	21.4	
Bed Size *				
Small	45.2	28.0	4.8	32.6
Medium	24.3	28.7	21.4	46.9
Large	30.6	43.3	73.8	20.5
Hospital Control *				
Public	18.2	0.0	0.0	
Non-profit	18.3	3.7	100.0	
Proprietary	15.5	0.0	0.0	
Private	12.9	4.2	0.0	
Collapsed	35.1	92.0	0.0	
Hospital Teaching Status				
Teaching	18.2	100.0	100.0	
Case Mix Index				
Mean (SD)	1.18 (0.001)	1.25 (0.001)	1.64 (0.18)	

* Bed size and hospital control were categorized differently for each data source (see methods).

REFERENCES

1. Schwaber MJ, Carmeli Y. Carbapenem-resistant Enterobacteriaceae: a potential threat. *JAMA*. 2008;300(24):2911.

2. Yigit H, Queenan AM, Anderson GJ, et al. Novel carbapenem-hydrolyzing {beta}-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. *Antimicrob Agents Chemother*. 2001;45(4):1151.

3. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. *Antimicrob Agents Chemother*. 2008;52(3):1028.

4. Gasink LB, Edelstein PH, Lautenbach E, Synnestvedt M, Fishman NO. Risk Factors and Clinical Impact of *Klebsiella pneumoniae* Carbapenemase-Producing *K. pneumoniae*. *Infection Control and Hospital Epidemiology*. 2009;30(12).

5. Bratu S, Landman D, Haag R, et al. Rapid spread of carbapenem-resistant Klebsiella *pneumoniae* in New York City: a new threat to our antibiotic armamentarium. *Arch Intern Med*. 2005;165(12):1430.

6. Hong T, Moland ES, Abdalhamid B, et al. *Escherichia coli*: development of carbapenem resistance during therapy. *Clin Infect Dis*. 2005;40(10):e84-6.

7. Vitti D, Protonotariou E, Sofianou D. Carbapenem-resistant *Escherichia coli* carrying the blaVIM-1 gene in the community. *Int J Antimicrob Agents*. 2009;34(2):187-188.

8. Lepape A, Monnet DL, participating members, European Society of Intensive Care Medicine. Experience of European intensive care physicians with infections due to antibiotic-resistant bacteria, 2009. *Euro Surveill*. 2009;14(45):19393.

9. Borer A, Saidel-Odes L, Riesenberg K, et al. Attributable Mortality Rate for Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia. *Infection Control and Hospital Epidemiology*. 2009;30(10).

10. Hussein K, Sprecher H, Mashiach T, Oren I, Kassis I, Finkelstein R. Carbapenem resistance among *Klebsiella pneumoniae* isolates: risk factors, molecular characteristics, and susceptibility patterns. *Infect Control Hosp Epidemiol*. 2009;30:000-000.

11. Kelesidis T, Karageorgopoulos DE, Kelesidis I, Falagas ME. Tigecycline for the treatment of multidrug-resistant Enterobacteriaceae: a systematic review of the evidence from microbiological and clinical studies. *J Antimicrob Chemother*. 2008.

12. Benenson S, Navon-Venezia S, Carmeli Y, et al. Carbapenem-resistant *Klebsiella pneumoniae* endocarditis in a young adult: Successful treatment with gentamicin and colistin. .

13. Cobo J, Morosini MI, Pintado V, et al. Use of tigecycline for the treatment of prolonged bacteremia due to a multiresistant VIM-1 and SHV-12 β-lactamase–producing *Klebsiella pneumoniae* epidemic clone. *Diagnostic Microbiology & Infectious Disease*. 2007.

14. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infection Control and Hospital Epidemiology*. 2008;29(12):1099-1106.

15. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. *Infect Control Hosp Epidemiol*. 2008;29(11):996-1011.

16. University HealthSystem Consortium. Clinical Data Base Glossary of Shared Data Definitions V2.0. 2007.

17. Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUP). Introduction to the HCUP Nationwide Inpatient Sample (NIS). . 2009. http://www.hcup-us.ahrq.gov/db/nation/nis/NIS_2007_INTRODUCTION.pdf.

18. Agency for Healthcare Research and Quality. HCUP NIS Description of Data Elements: DXn - Diagnosis. . http://www.hcup-us.ahrq.gov/db/vars/dxn/nisnote.jsp. Updated 20082010.

19. Rothman KJ. *Modern epidemiology*. Boston: Little, Brown; 1986.

20. Agency for Healthcare Research and Quality. HCUP NIS Description of Data Elements: HOSP_CONTROL - Control/ownership of hospital. . http://hcup-us.ahrq.gov/db/vars/hosp_control/nisnote.jsp. Updated 20082010.

21. Centers for Medicare and Medicaid Services. Acute Inpatient Files for Download: Details for DRG Relative Weights. http://www.cms.gov/AcuteInpatientPPS/FFD/itemdetail.asp?filterType=%20none&filterByDID=99&sortByDID=2&sortOrder=ascending&itemID=CMS061850&intNumPerPage=%2020002010.

22. Kuster SP, Ruef C, Bollinger AK, et al. Correlation between case mix index and antibiotic use in hospitals. *J Antimicrob Chemother*. 2008;62(4):837.

23. Chou AF, Yano EM, McCoy KD, Willis DR, Doebbeling BN. Structural and process factors affecting the implementation of antimicrobial resistance prevention and control strategies in US hospitals. *Health Care Manage Rev*. 2008;33(4):308.

24. Flach SD, Diekema DJ, Yankey JW, et al. Variation in the use of procedures to monitor antimicrobial resistance in U.S. hospitals. *Infect Control Hosp Epidemiol*. 2005;26(1):31-38.

25. Ward MM, Diekema DJ, Yankey JW, et al. Implementation of strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in U.S. hospitals. *Infect Control Hosp Epidemio*l. 2005;26(1):21-30.

26. Keeler EB, Rubenstein LV, Kahn KL, et al. Hospital characteristics and quality of care. *JAM*A. 1992;268(13):1709-1714.

27. Hartz A, Krakauer H, Kuhn E, et al. Hospital characteristics and mortality rates. *N Engl J Me*d. 1989;321(25):1720.

28. Diekema DJ, BootsMiller BJ, Vaughn TE, et al. Antimicrobial resistance trends and outbreak frequency in United States hospitals. *Clinical infectious disease*s. 2004;38:78-85.

29. Kwak YG, Choi SH, Choo EJ, et al. Risk factors for the acquisition of carbapenem-resistant *Klebsiella pneumoniae* among hospitalized patients. *Microbial Drug Resistanc*e. 2005;11(2):165-169.

30. Effler P, Ching-Lee M, Bogard A, Ieong MC, Nekomoto T, Jernigan D. Statewide system of electronic notifiable disease reporting from clinical laboratories: comparing automated reporting with conventional methods. *JAM*A. 1999;282(19):1845.

31. Silk BJ, Berkelman RL. A review of strategies for enhancing the completeness of notifiable disease reporting. *Journal of Public Health Management and Practic*e. 2005;11(3):191.

32. Srinivasan A, Patel JB. *Klebsiella pneumoniae* carbapenemase-producing organisms: an ounce of prevention really is worth a pound of cure. *Infection Control and Hospital Epidemiolog*y. 2008;29(12):1107-1109.

33. Anderson K, Lonsway D, Rasheed J, et al. Evaluation of methods to identify the *Klebsiella pneumoniae* carbapenemase in Enterobacteriaceae. *J Clin Microbio*l. 2007;45(8):2723.

34. Schechner V, Straus-Robinson K, Schwartz D, et al. Evaluation of PCR-Based Testing for Surveillance of KPC-Producing Carbapenem-Resistant Members of the Enterobacteriaceae Family. *J Clin Microbio*l. 2009;47(10):3261.

35. Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. *The Lancet Infectious Disease*s. 2009;9(4):228-236.