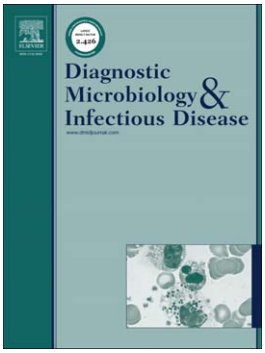

Carbapenem-resistant *Enterobacteriaceae* and the Correlation between Carbapenem and Fluoroquinolone Usage and Resistance in the U.S. Military Health System

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Carbapenem-resistant *Enterobacteriaceae* and the Correlation between Carbapenem and Fluoroquinolone Usage and Resistance in the U.S. Military Health System

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DISCLAIMER: The views expressed herein are solely those of the authors and not to be construed as official or representing those of the U.S. Army or the Department of Defense.

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Abstract:

Whether carbapenem or fluoroquinolone usage is correlated with carbapenem resistant Enterobacteriaceae has not been investigated at the level of an entire U.S. nationwide managed healthcare system. We analyzed 75 million person-years of surveillance and 1,969,315 cultures from all 266 hospitals in the geographically dispersed U.S. Military Health System. Incidences of CRE remained under 1 case per 100,000 person-years. Incidences of CRE increased relative to 2005 baseline levels in 3 of 7 subsequent years, then decreased in 2012 ($P < 0.05$). Incident proportions of carbapenem resistance differed significantly among years, geographical regions, and bacterial species. Although use and resistance strongly correlated ($R > 0.80$) for several 'drug-bug' combinations, none were significant at the national or facility level. One exception was that inpatient consumption of fluoroquinolones was significantly correlated ($P = .0007$) with carbapenem resistance in E. coli when data from the major referral centers of the Southern and Northern regions were combined.

Key words: antibiotic use, antibiotic consumption, healthcare network, carbapenem resistance

1.0 Introduction

Enterobacteriaceae are leading causes of community and hospital acquired infections [1, 2]. Antibiotic resistance can rapidly develop and spread in these bacteria through mobile genetic elements readily shared among unrelated species [1, 2].

Carbapenem-resistant *Enterobacteriaceae* (CRE) have become an especially worrisome global public health crisis [1-5]. Infections caused by these bacteria can be associated with a mortality rate as high as 80% [2, 6, 7]. Carbapenem resistance (CR) often arises through mechanisms that involve acquisition of multiple drug resistance genes resulting in extremely-drug resistant or pan-drug resistant infections with few or no treatment options [1, 8].

Carbapenem-resistance is increasing world-wide [1, 2, 5], but the burden of such resistance in one large and diverse U.S. population, healthcare beneficiaries of the Department of Defense (DoD), has not been reported. Furthermore, there is conflicting evidence on whether increased antibiotic consumption, in particular of carbapenems and fluoroquinolones, is correlated with this increased resistance [9-15]. Of note, correlation between antibiotic consumption and resistance in *Enterobacteriaceae* throughout an entire healthcare system in the United States has not been reported [16].

Previous antibiotic exposure, especially to fluoroquinolones, was correlated with future isolation of CRE in individual patients in case-control studies [2, 17, 18]. Other studies have not found that association [12].

Our objectives were to determine the level of CRE in a geographically dispersed national managed care system, the health system of the DoD, and to determine if total carbapenem or fluoroquinolone consumption throughout the system was correlated with CR. We also provide proportions and rates, because the use of only one may not reflect the true burden of resistance or

loss of treatment options, and also because a report format most useful for the clinician treating empirically (proportions) may not be as useful to the public health professional (rates) [19-23].

2.0 Methods

This study was undertaken as a quality improvement initiative authorized by policy memoranda 09-050, 11-035, 13-016 and IRB protocol number #1812.

2.1 Population & Data Collection

The DoD has a managed care system composed of 266 fixed location medical facilities throughout the United States and overseas. It is divided into four geographic regions: North, South, West, and Pacific. The surveillance population, all DoD beneficiaries who were eligible to receive care from January 2005 through December 2012, included patients of all ages and races. There were approximately 9.7 million beneficiaries in 2012 and an average of 9.5 million yearly and the demographic details have been published previously [24]. The DoD uses electronic health records (EHR) for all clinical encounters. Methods used for extracting and aggregating microbiology data from EHR have been previously published [24], as have methods for isolate collection and characterization [25-26]. Briefly, from all positive cultures, only unique/deduplicated isolates, defined as the first *Enterobacteriaceae* (*E. coli*, *Enterobacter* spp. or *Klebsiella* spp.) isolate per patient per calendar year, were culled. From these, those non-susceptible to imipenem, meropenem, and/or doripenem, based on the prevailing Food and Drug Administration (FDA) and the 2010 Clinical Laboratory Standards Institute (CLSI) (M100-S20-U) susceptibility breakpoint defined by a minimum inhibitory concentration of >/=4 ug/ml, were extracted to calculate incident rates and proportions of CRE. This breakpoint was used for all the years, because the newest CLSI breakpoints released in 2012 (M100-S22) could not be universally adopted (across all years and all facilities) for this study. Workload-tracking and billing location codes were used to determine if the culture originated from an inpatient or outpatient care area. Correlation tests were performed several

ways: one set of tests used aggregate data from the entire DoD (system level); the second series of tests used data from U.S. domestic facilities, stratified by geographic region (regional level); the third set of analyses focused on data from the two busiest and largest referral centers in the DoD, presumably where the most carbapenems and fluoroquinolones are prescribed and the resistance occurs (facility level). For system level data, we examined correlations between antibiotic usage and a) incidence rates, b) incident proportions, and c) absolute numbers of resistant isolates. These tests were performed for CREs as a whole, as well as for *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. separately. At the regional and facility levels we measured correlations between antibiotic usage and incident proportions and between usage and absolute numbers of CR isolates.

For antibiotic consumption at the major referral facilities, the unit of measure was physician orders or prescriptions written for each antibiotic. For regional level usage, and usage across the entire system, doses given and/or for outpatient usage, purchases invoiced were used. In terms of a defined daily dose (DDD), this unit would approximately equate to a fraction of the defined daily dose (DDD) depending on the average recommended daily dose based on normal renal function. For example, for a patient with normal creatinine clearance who received the antibiotic for a full 24 hr. period, one unit would equate to 1/3 the usual meropenem, DDD, or ¼ the usual imipenem DDD. Meropenem is usually dosed every eight hours, and imipenem every six.

2.2 Statistics

Statistical tests were performed using the R version 2.14 software package (http://cran.us.r-project.org/). For ANOVA analysis of U.S. regional data, we used the *aov* and *TukeyHSD* functions. For data collected across the entire military healthcare system (US and overseas facilities) pairwise comparisons of rates and proportions were performed using Fisher's exact test, trends were analyzed using the Chi squared proportion trend test, and usage-resistance

relationships were analyzed using the Pearson correlation test. P values were adjusted for multiple testing using the Bonferroni correction.

3.0 Results

3.1 Overall Burden of Carbapenem Resistance

During 2005-2012, there were 75,529,012 person-years of surveillance and 1,969,315 bacterial organisms identified from 1,823,030 clinical cultures. Those organisms included 667,004 *Enterobacteriaceae,* of which 368 were classified as CRE for an overall incident proportion of 0.487% (95% CI: 0.439-0.540) (Table 1). 77% (284) were isolated in outpatient care areas, and 23% (84) were isolated from inpatient care areas. The mean annual incident rate of CRE for this period was 0.49 per 100,000 patient years (Table 1).

3.2 Proportions

The proportion of all *Enterobacteriaceae* that were carbapenem resistant rose from 0.033% in 2005 to 0.052% in 2012 (P = 0.053) (Figure 1). Combining all species and using 2005 as the reference year, incidence proportions of CRE increased significantly in 3 of 7 subsequent surveillance years, with the most significant increase occurring in 2010 (P < 0.0001) (Figure 1). Considering species separately, CR in *E. coli* also showed a statistically significant increase in 3 of 7 surveillance years compared to the baseline in 2005. CR in *Klebsiella* spp. (*K. pneumoniae and K. oxytoca*) reached a maximum in 2010 (P = 0.035). CR in *Enterobacter* spp. (*E. cloacae* and *E. aerogenes*) fluctuated the most and showed no significant trend (Figure 1). The lowest proportion of incident resistance (0.020%) was seen in *E. coli* in 2005 and the highest (0.243%) was seen in *Enterobacter* spp. during 2012. The decrease in the proportion of all CRE from the peak year of 2010 to 2012 was significant (P = 0.048). Among *Enterobacteriaceae, Klebsiella* spp. showed the fastest increase in the proportion resistant to carbapenems, as measured by linear regression (Online Supplemental Figure 1).

3.3 Rates

Incidence rates of all CRE combined varied from a low of 0.335 per 100,000 person years in 2005 to a high of 0.672 in 2010 (P = 0.001) (Table 1). Relative to 2005, the reference year, rates of CR in *E. coli* were significantly higher in 2009 and 2010 (Figure 2). The lowest rate (0.043) was seen in *Enterobacter* spp. in 2008, and the highest rate was seen in *E coli* (0.455) in 2010. *E. coli* had the fastest increase in CR rate from 2005-2012 (Online Supplemental Figure 2).

3.4 Factors affecting the likelihood of CR

To see which variables were associated with the probability that an organism was carbapenem resistant we performed ANOVA on the regional data set. The analysis was performed two ways: a) the correlation of year, region and organism to incident proportion were examined individually; b) all variables were examined together, sequentially controlling for organism, then region, then year. Region and organism were highly significant factors (P <0.0001). The year of isolation showed a lesser, though statistically significant association, after controlling for region and organisms (data not shown).

Tukey's HSD test was used to discover which specific pairs of regions, organisms and years had significantly different incidence proportions. Examination of CR incident proportion by species revealed significant differences between E. coli and Enterobacter spp. (P < 0.001) and *E. coli* and *Klebsiella* spp. (P < 0.001) but not between *Enterobacte*r and *Klebsiella* (P = 0.06) (Figure 3 and other data not shown). When we analyzed the relationship between geographical region and CR, we found carbapenem resistance proportions differed significantly between every pair of regions except between West and Pacific (Figure 3). The South had the highest incidence of resistance; the West and Pacific had the lowest. Examining carbapenem resistance incidence proportions by year showed that overall CR incidence in 2010 was significantly higher than in

2005 and 2008. No other difference in annual incident proportions was statistically significant (Figure 3).

We next asked whether differences in regional incident proportions remained significant after controlling for species differences. CR incidence in Klebsiella varied the least between geographical regions, and E. coli differed the most (data not shown). A similar analysis demonstrated statistically significantly yearly variation in *E. coli* carbapenem resistance incidence (data not shown).

3.5 Antibiotic consumption:

The earliest year for which system level (enterprise wide) antibiotic usage data were available is 2008 (Supplemental Table 1A-B). Carbapenem consumption ranged from a low of 8,023 units in 2009 to a high of 12,965 units in 2011. Between 2008 and 2012 carbapenem consumption increased by 32%. Fluoroquinolone consumption ranged from a low of 158,145 units in 2011 to a high of 245,765 units in 2012. From 2008 to 2012 fluoroquinolone consumption within the DOD increased by 17%. For the major referral centers in the North and South regions we further stratified carbapenem and fluoroquinolone usage into inpatient and outpatient doses (Supplemental Figure 3). Peak consumption in these two facilities occurred slightly before peak consumption throughout the entire enterprise, with peak carbapenem and fluoroquinolone consumption occurring between 2010 and 2011. (Supplemental Figure 3 and Supplemental Tables 1A -B and Supplemental Table 2).

3.6 Correlation between usage and resistance

At the enterprise level, there was no significant correlation between carbapenem usage and the proportions or rates of resistance for any organism (*E. coli*, *Klebsiella* spp., *Enterobacter* spp.) (Supplemental Table1C). Likewise, carbapenem consumption was not correlated with proportions or rates of CRE among all *Enterobacteriaceae* combined. Similarly,

fluoroquinolone consumption was not correlated with carbapenem resistance in individual species groups or in all CRE combined (Supplemental Table 1C). At the major referral center of the South region, use was strongly correlated (R > 0.85) with resistance for certain 'drug-bug' combinations. For example, inpatient use of carbapenems correlated with resistance in all *Enterobacteriaceae* combined (R = 0.94; P = 0.05), and inpatient use of fluoroquinolones correlated with carbapenem resistance in *E. coli* (R = 0.91; P = 0.08) However, no correlation maintained statistical significance after multiple test correction (Supplemental Table 2). Antibiotic consumption and incidence proportions of CRE were not strongly correlated at the major North regional referral center When data from both referral centers were combined, however, inpatient use of fluoroquinolone was significantly correlated with carbapenem resistance and remained so after multiple test correction (R = 0.85; P = 0.007) (Supplemental Table 2).

4.0 Discussion

With nearly 2 million clinical cultures and 75 million person-years of surveillance, our report is one of the largest to date (Table 2). Proportions and rates of all CRE combined peaked in 2010, with the increase in overall resistance being driven by increases in resistant *E. coli*. Carbapenem and fluoroquinolone usage were correlated with resistance in certain stratified analyses, but the only statistically significant association was a positive correlation between inpatient fluoroquinolone use and carbapenem resistance in *E. coli* isolated at the North and South regional referral centers. Except for the Meropenem Yearly Susceptibility Test Information Program (MYSTIC) report (a study limited to 6-10 U.S. hospitals during 1999-2001 which collected antibiotic consumption data using surveys rather than information drawn from centralized databases) [9], and a small single center facility [27], we found no other U.S. studies that observed a correlation between carbapenem resistance with fluoroquinolone or carbapenem

consumption. No other U.S. reports examined consumption-resistance relationships in *Enterobacteriaceae* in a nationwide managed care network [16]. The smaller studies that evaluated the relationship between antimicrobial use and resistance reported varying results [9-13,15, 27]. Dissimilar results can be explained by different populations, time lag, length of surveillance, and the definitions of usage [9]. Although DDD is the most widely used measure of consumption, it represents an assumed average dose per day for primary adult drug indication and has several limitations [9, 28]. In three Dutch communities, antibiotic usage differed significantly, but resistance rates in *E. coli* did not [10]. A study from Taiwan also reported that increased usage of carbapenems was not associated with an increase in resistance to carbapenems in *Enterobacteriaceae* [11]. In addition to being consistent with the above studies, our data agreed with the MYSTIC report, which showed that proportions of CRE were low (<1%), and that carbapenem usage was not correlated with resistance to carbapenem [9]. However, data from Europe suggests that total antibiotic consumption is directly correlated with resistance in carbepenemase producing - *K. pneumoniae*. For example, Greece has both the highest usage and percent of carbepenemase producing *Klebsiella pneumoniae*, while the Netherlands has the lowest usage rates and percent resistance [14]. Unlike Europe, the U.S. has no comparable data system for measuring antibiotic consumption and resistance profiles across states [14, 29].

The lack of a correlation between drug consumption and resistance might be due to the length of the study period. However, previous studies showed that 5 years of surveillance was adequate, and a 1 year lag between peak usage and peak resistance was often observed [22].

Proportions and rates in our study were lower than in other U.S. populations and networks [4, 23, 30, 31]. One reason for this observation might be that a lower proportion of our isolates or data came from long term acute care facilities, known reservoirs of CRE [2, 32, 33]. Although

patients in the military health system are thought to be younger and healthier, the population in the military is fairly reflective of the age and sex distribution in the general population due to the presence of retirees and family members who are also eligible for care.[24] Second, the definition of 'unique' isolate in our study is more stringent than the definition used in other reports [30].

EARSNET reported increasing CRE trends in Greece, Cyprus, Hungary and Italy, but decreasing trends in Germany and Norway (Table 1) [34]. Previously, the NHSN reported and increasing trend in CRE among health care associated infections, where 8% of *Klebsiella* spp. were carbapenem-resistant in 2007, compared with <1% in 2000 [35]. However, in a later report, the proportion of carbapenem resistant isolates reported to the NHSN did not change significantly from 2007-2010 [4]. In a recent report published this August, the rate of CRE detection in a network of community hospitals in the Southeastern United States increased more than five-fold from 2008 to 2012 [36].

Our study has several limitations. First, pairwise comparison between yearly data might not be able to detect short-term variation. Trend analysis is more robust if there are more data points. However, CRE were uncommon, so the number of cases in most months would be too low for statistical analysis. Furthermore, the annual data encompasses monthly and seasonal variation. Therefore, if we detected differences over time in seasonal data, but not annual data, positive correlations between usage and rate/incidence in some seasons would be cancelled out by negative correlations between usage and rate/incidence at other times of the year. Second, our findings may not be generalizable to civilian healthcare systems or other large managed care networks. However, the DoD population includes patients of all ages and races from primary care clinics to tertiary teaching and referral centers [24]. Third, it is nearly impossible to get precise patient-days, patient-years of antibiotic usage, and usage in milligrams for an entire healthcare system,

because even with electronic medical records, manual chart review is required to determine the exact start and stop times for each antibiotic prescription. However, our goal was not to have a standard for comparing antibiotic usage across systems or countries. Instead, our goal was to see whether usage correlated with resistance in a single large, geographically dispersed healthcare system. The increase in fluoroquinolone consumption between 2011 and 2012 was large and cannot be explained with certainty. Factors that could have contributed to this increase include increased prescribing of these agents for preemptive self-treatment of traveler's diarrhea to Africa and Asia. (During that period military exercises in those areas increased.) Also during this period bacterial infections not successfully treated with first line agents were being observed at an increasing frequency. Other reasons include ease of use (once or twice per day and intravenous to oral conversions) and poor stewardship of antibiotics. Finally**,** all DoD hospitals use automated micro-broth susceptibility analyzers and the results from these instruments are what is entered in the EHR. Therefore the definitions of resistance are restricted to the 2010 CLSI and the prevailing FDA susceptibility breakpoints, which are pre-programmed in these analyzers. We could not apply the 2012 CLSI breakpoints universally in this study. Since updates to susceptibility breakpoints are modified over time, and at different intervals according to facility and agency, trending the burden of resistance across years and geographic areas is extremely difficult. A recent study illustrates this difficulty in that only 5 of 25 hospitals in a surveillance network were able to adopt even the older 2010 CLSI breakpoints for a surveillance study conducted during a similar period (2008-2012) as this study [36]. To mitigate this we have developed a computer program that permits users to apply different sets of susceptibility breakpoints 'on the fly' to see how breakpoints from different agencies would affect their results. This program runs on all computers and is available free of charge. If we substitute the most recent CLSI 2012 breakpoints for our definition of resistance, the incident proportions would likely be higher. However, it is not known if that apparent increase reflects an

increase in the true burden as manifested by a reduction in treatment options [20]. A recent study reported that detection rates of CRE significantly increased when 2010 CLSI breakpoints were used instead of 2007 CLSI breakpoints (4.1 vs 0.5 per 100, 000 patient days; p<.001). However, the impact of the newer 2012 breakpoints was not investigated in that study. To estimate the effect the 2012 breakpoints would have in our study, we analyzed the database in a repository of over 25,000 centrally characterized MDR- ESKAPE pathogens from a growing number of DoD hospitals, which are representative of the 266 hospitals in this study [37]. All *Klebsiella* and *Enterobacter* spp, along with all *E. coli* collected during the same time period of this study (2005-2013) (n=4016) were included in the analysis. Using the 2010 CLSI breakpoints34% (1357) were classified as carbapemem resistant, whereas 49% (1955) were resistant according to the 2012 CLSI breakpoints.

In conclusion, numerous factors confound antimicrobial usage-resistance relationships. Our findings should not be interpreted as a diminishment of the crucial need for antimicrobial stewardship and thoughtful prescribing. On the contrary, our findings highlight the importance of using fluoroquinolones judiciously. This study provides a baseline for trending changes in disease burdens and the interactions between susceptible and resistant bacteria populations, which is important for quantifying the health economic effects of such programs and efforts [38]. That CRE are still relatively uncommon in this population presents a special opportunity for early preventive interventions [2, 4]. Surveillance should continue, with the identification of CRE from a clinical culture prompting an aggressive response to prevent further transmission [2, 4]. Ongoing surveillance and research are needed.

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Figure Legends:

Figure 1: Incidence proportions. Annual incidence proportions of CRE in the military healthcare system. The 95% confidence interval is indicated by a vertical line at the top of each histogram bar. The red horizontal line indicates the incidence proportion for 2005. Numbers above each bar indicate the unadjusted P-value for the change in proportion from 2005. The number in parentheses above the 2012 incidence bar indicates the unadjusted P-value for the change in proportion from 2010 to 2012. An asterisk indicates that a P-value is significant after correction for multiple comparisons (n=6).

Figure 2: Incidence rates. Annual incidence rates of CRE in the military healthcare system.

Figure 3: Major factors associated with CRE incidence. Incidence proportions of total CRE plotted by year (A), geographical region (B) and year (C). The 95% confidence interval is indicated by a vertical line at the top of each histogram bar. Pairs of years, regions and organisms with significantly different (corrected P <= 0.05) have the same symbol above the histogram bar (e.g. 2005 compared to 2010 and 2008 compared to 2010).

Table 1: Incidence Rates & Proportions of Carbapenem-resistant *Enterobacteriaceae* in the U.S. Department of Defense Health System

	2005			2006			2007			2008			2009			2010			2011			2012			All Years Combined		
# of patients per year Incidence rate (95% CI)	9248940 0.335 (0.228-0.476)			9190266 0.490 (0.357-0.655)			9197758 0.424 (0.302-0.580)			9347645 0.439 (0.315-0.595)			9556878 0.607 (0.461-0.785)			9671583 0.672 (0.519-0.857)			9662508 0.528 (0.393-0.694)			9653434 0.394 (0.279-0.540)			75529012 0.487 (0.439-0.540)		
Species	Total	Incidence		Total	Incidence		Total	Incidence		Total	Incidence		Total	Incidence		Total	Incidence		Total	Incidence		Total	Incidence		Total	Incidence	
		#	% (CI)		#	% (CI)		#	% (CI)		#	% (CI)		#	% (CI)		#	% (CI)		#	% (CI)		#	% (CI)		#	% (CI)
Klebsiella spp.	9972	7	0.070 (0.065-0.076)	9639	9	0.093 (0.087-0.100)	8427	8	0.095 (0.088-0.102)	9501	10	0.105 (0.099-0.112)	9149	11	0.120 (0.113-0.128)	8691	16	0.184 (0.175-0.193)	8589	13	0.151 (0.143-0.160)	8376	10	0.119 (0.112-0.127)	72344	84	0.116 (0.093-0.144)
E. coli	80473	16	0.020 (0.019-0.021)	77132	29	0.038 (0.036-0.039)	65501	24	0.037 (0.035-0.038)	73282	27	0.037 (0.035-0.038)	71150	38	0.053 (0.052-0.055)	68881	44	0.064 (0.062-0.066)	63639	31	0.049 (0.047-0.050)	61488	21	0.034 (0.033-0.036)	561546	230	0.041 (0.036-0.047)
Enterobacter spp.	4392	8	0.182 (0.170-0.195)	4226	7	0.166 (0.154-0.178)	3821	7	0.183 (0.170-0.197)	4128	4	0.097 (0.088-0.107)	4045	9	0.222 (0.208-0.238)	4576	5	0.109 (0.100-0.119)	5041	7	0.139 (0.129-0.150)	2885	7	0.243 (0.225-0.261)	33114	54	0.163 (0.123-0.213)
Total	94837	31	0.033 (0.022-0.046)	90997	45	0.049 (0.036-0.066)	77749	39	0.050 (0.036-0.069)	86911	41	0.047 (0.034-0.064)	84344	58	0.069 (0.052-0.089)	82148	65	0.079 (0.061-0.101)	77269	51	0.066 (0.049-0.087)	72749	38	0.052 (0.037-0.072)	667004	368	0.055 (0.050-0.061)
Stratified by inpatient / or outpatient		11 20			7 38			10 29			6 35			13 45			15 50			11 40			11 27			84 284	

Table 2. Resistance Trends in the Largest U.S. and European Studies of Carbapenem-resistant *Enterobacteriaceae*

Scope & Period	Denominator[1]	Numerator(s)	Measurement	Result	Reference
266 U.S Hospitals (inc. Alaska Hawaii, and Germany) 2005; 2008-2012	1,969,315	667,004 Enterobacteriaceae	Proportion and Rate	Increase in Proportion Stable rates	This study
2,039 U.S. Hospitals 2009-2010 vs.2007-2008	81,131	19,642 Enterobacteriaceae	Proportion	Stable	Sievert et al. 2013
14 Hospitals in Europe 1998-2007	36,679	10,241 Enterobacteriaceae	Rate	Increase	Ammerlaan et al. 2013
12 U.S. medical centers 1998-2008	27,289	13,001 Enterobacteriaceae	Rate	Stable	Rhomberg et al. 2009
287 clinical laboratories in the US 1999-2010	500,000 K. pneumonia isolates	5,558 Carbapenem resistant K. pneumoniae	Proportion	Increase	Braykov et al. 2013
200 US Hospitals 1998-2010	187,359 Klebsiella spp.	8,056 Carbapenem resistant K. pneumoniae	Proportion	Increase	Sanchez et al. 2013
28 Countries in Europe 2008-2011	14,549 K pneumoniae 59,326 E. coli	1,323 Carbapenem resistant K. pneumoniae 24 Carbapenem Resistant E. coli	Proportion	Increase for K. pneumoniae in 3 countries Increase for E. coli in 13 countries	EARSNET 2011
69 Laboratories in LA, CA 2010-2011	814 case reports of suspected carbapenem resistant K. pneumoniae infections	675 confirmed cases of carbapenem resistant K. pneumoniae infections	Rate	Emerging and high in long term acute care settings	Marquez et al. 2013
83 Medical centers in USA, Europe and Latin America 2007-2009	15,948 E. coli and Klebsiella spp	Carbapenem resistant and Carbapenemase producing E. coli and Klebsiella spp	Rate	Increase	Castanheira et al. 2011

1 Total number of isolates examined for the study

Figure 1

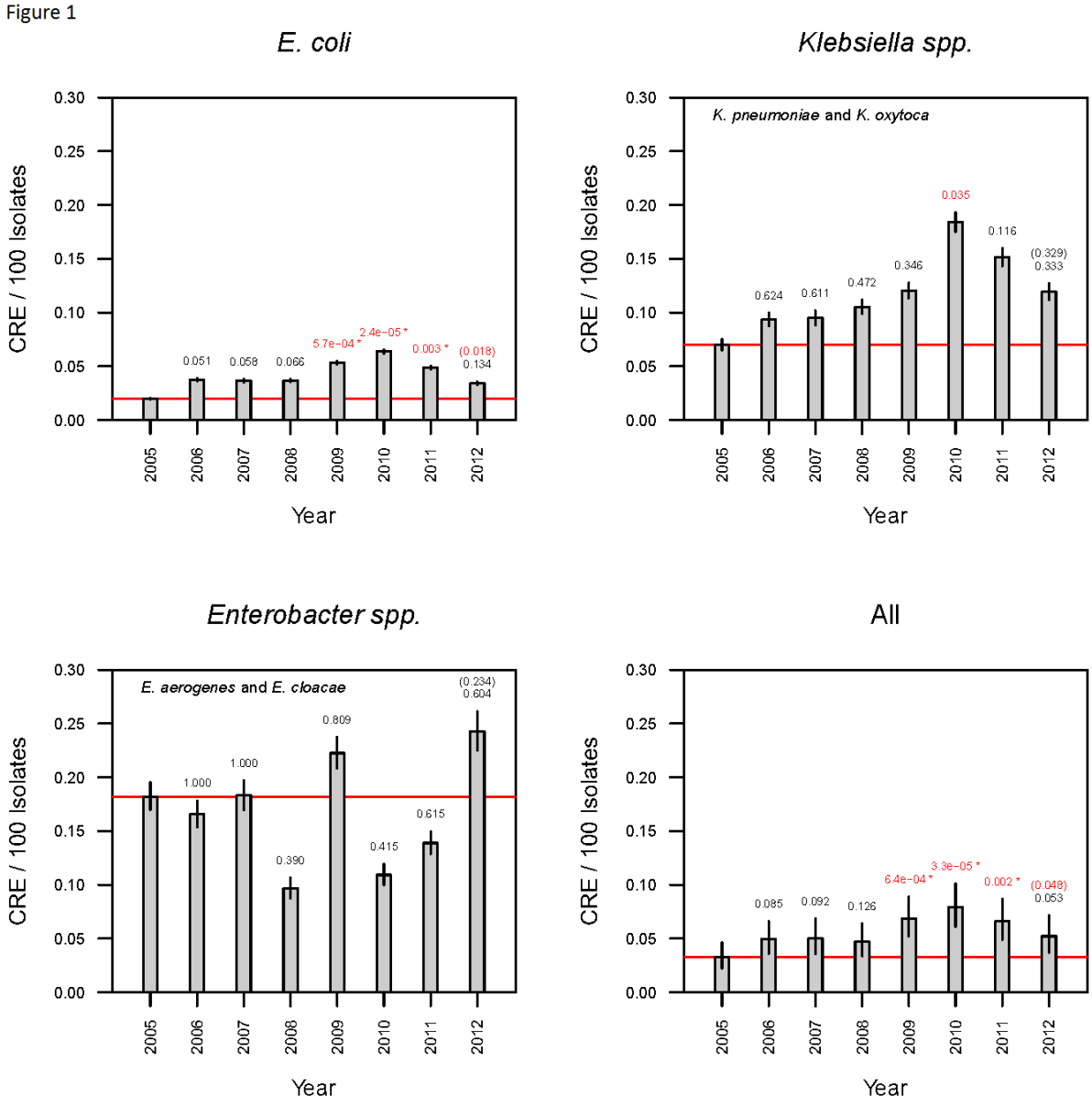


Figure 2: Annual CRE Incidence Rates

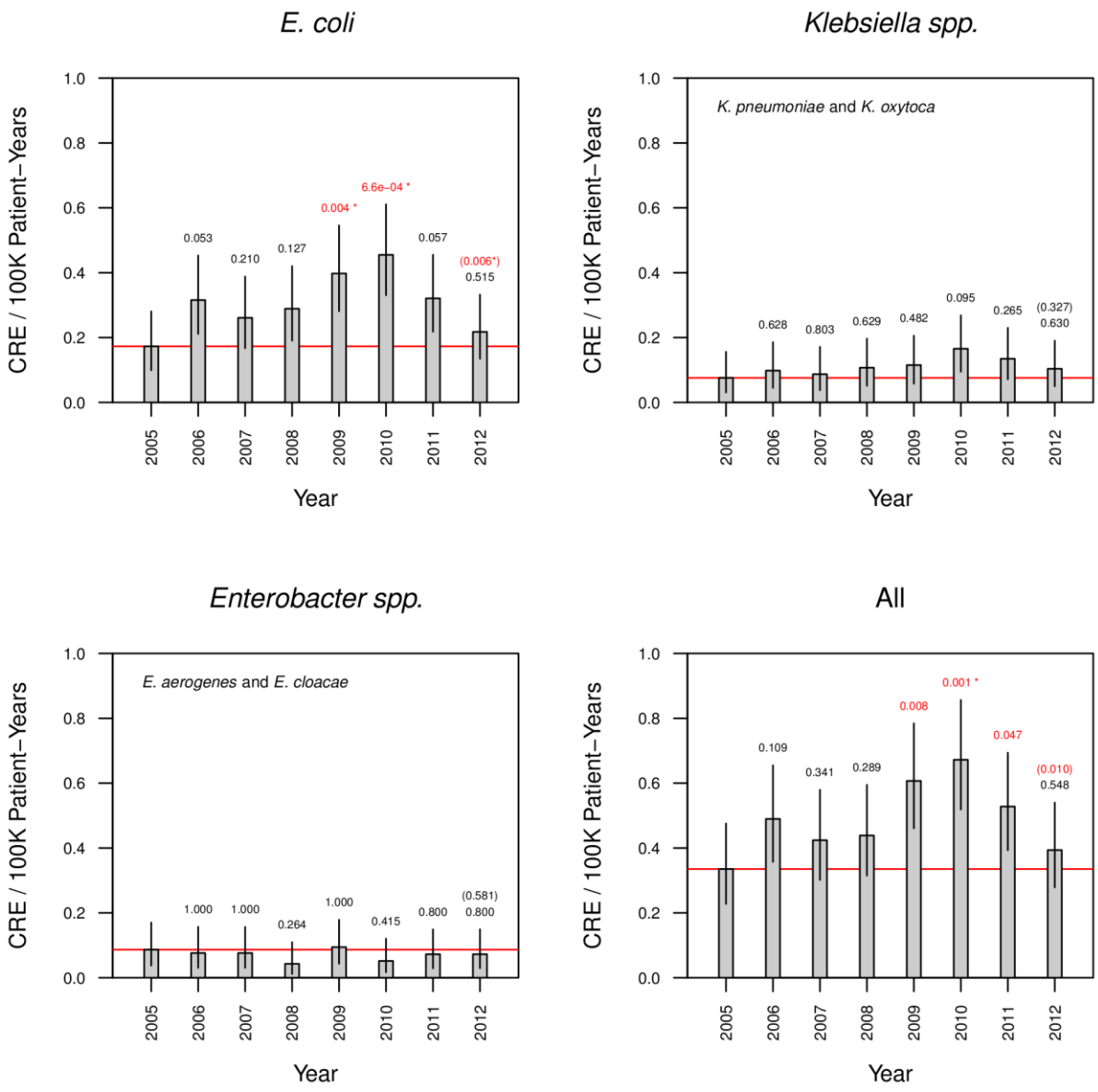
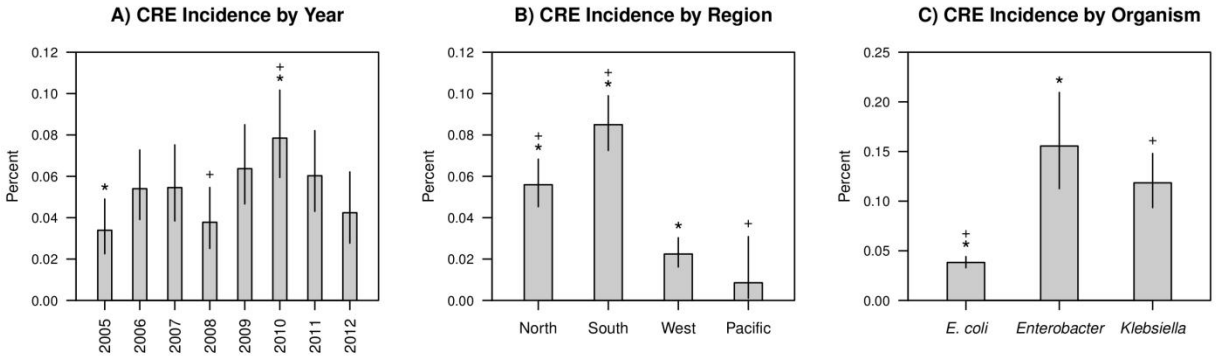


Figure 3: Major Factors Associated with CRE Incidence



Highlights

- In the healthcare system, carbapenem and quinolone use increased.
- Incidences of carbapenem resistant Enterobacteriaceae increased, then decreased.
- Inpatient consumption of fluoroquinolones correlated with carbapenem resistance.
- Incidences of resistance and drug consumption may be too low for correlation.
- This is the largest such use/resistance correlation study in the U.S. to date.