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DEVELOPMENT AND COMPARISON OF RISK-ADJUSTED MODELS TO BENCHMARK ANTIBIOTIC USE IN THE UNIVERSITY HEALTHSYSTEM CONSORTIUM HOSPITALS

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A dissertation submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy at Virginia Commonwealth University

by

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Dedication

I would like to dedicate this dissertation to

My mother, Asma' Kilani, for dedicating her life to me and my siblings and being the best mom anyone could ask for.
I am eternally grateful for all that you have done for me…

My late father, Professor Mohammed Ibrahim, I may never become the brilliant scholar you were but I hope I have done you proud.
Rest in peace Dad…

My wife, Ghadeer Dawwas, your love, support and devotion have carried me through many difficult times and sleepless nights. Time for a new chapter my darling…

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My father, Professor Mohammed Ibrahim, passed away when I was only 10 years old and his untimely departure from this world inflicted a gaping wound upon me that has not and will never heal. He was a loving and caring father who instilled in me a passion for learning by constantly buying me books and encouraging me to read them. He is my role model and I will always strive to emulate his aptitude and scholarly excellence knowing that I may well fall short. I would not be where I am today had he not paved the way for me. Until we meet again, may God rest your soul Dad.

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List of Abbreviations

Abbreviation	Description	Abbreviation	Description
AbC	Antibacterial Consumption	IPPS	Inpatient Prospective Payment System
AIC	Akaike information criteria	IQR	Inter-quartile range
AICc	Corrected Akaike information criteria	ISR	Indirectly standardized rate
ANCOVA	Analysis of covariance	LOOCV	Leave-one-out cross validation
APR-DRGs	All Patient Refined Diagnosis Related Groups	LOS	Length of stay
AR	Attributable risk	LOT	Length of therapy
ASP	Antimicrobial stewardship program	MLR	Multivariable linear regression
ATC	Anatomical Therapeutic Chemical	MS-DRGs	Medicare Severity Diagnosis Related Groups
BLUE	Best linear unbiased estimator	MSE	Mean square error
BSI	Bloodstream infection	OLS	Ordinary least squares
CDC	Centers for Disease Control and Prevention	PDs	Patient days
CI	Confidence interval	PDD	Prescribed daily dose
CMI	Case-mix index	RDD	Recommended daily dose
CMS	The Centers for Medicare and Medicaid Services	PRESS	Predicted residual error sum of squares
CRM	Clinical Resource Manager	RR	Relative risk
CSL	Clinical service line	RW	Relative weights
DDD	Defined daily dose	SD	Standard deviation
df	Degrees of freedom	SHEA	Society for Healthcare Epidemiology of America
DOTs	Days of therapy	SIR	Standardized incidence ratio
DRGs	Diagnosis related groups	SMR	Standardized mortality ratio
DSR	Directly standardized rate	SOI	Severity of illness
DUR	Drug utilization review	SSE	Error sum of squares
GV	Generalized variance	SST	Total sum of squares
HAI	Healthcare-associated infection	SSR	Regression sum of squares
HCFA	Health Care Financing Administration	UHC	University Health System Consortium
HIV	Human immunodeficiency virus	UMVUE	Uniformly minimum-variance unbiased estimator
ICARE	Intensive Care Antimicrobial Resistance Epidemiology	UTI	Urinary tract infection
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*	VIF	Variance inflation factor
ICU	Intensive care unit	VRE	Vancomycin-resistant enterococci
ID	Infectious diseases	WHO	World Health Organization
IDSA	Infectious Diseases Society of America		

Abstract

DEVELOPMENT AND COMPARISON OF RISK-ADJUSTED MODELS TO BENCHMARK ANTIBIOTIC USE IN THE UNIVERSITY HEALTH SYSTEM CONSORTIUM HOSPITALS

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Background. Infectious diseases societies recommend that hospitals risk-adjust their antimicrobial use before comparing it to their peers, a process called benchmarking. The purpose of this investigation is to apply and compare 3 risk-adjustment procedures for benchmarking hospital antibacterial consumption (AbC). Two standardization of rates procedures,

direct and indirect standardization, are compared with one another as well as with regression modeling.

Methods. Total aggregate adult AbC for 52 systemic antibacterial agents was measured in 70 hospitals that subscribed to the University HealthSystem Consortium Clinical Resource Manager database in 2009 and expressed as days of therapy (DOTs) per either 1000 patients days (PDs) or 1000 discharges. The two AbC rates served the role of the outcome while several known risk factors for AbC served the role of potential predictor variables in the linear regression models. Selection criteria were applied to select a model that represented the first rate (Model I) and another that represented the second (Model II), respectively, and outliers were identified. Adult discharges in each hospital were then stratified into 35 clinical service lines based upon their Medicare Severity-Diagnosis Related Group (MS-DRG) assignment. Direct and indirect standardization were applied to this set and the expected-to-observed (E/O) and observed-to-expected (O/E) ratios, respectively, for AbC were determined. The agreement of the different methods in ranking hospitals according to their risk-adjusted rates and in identifying outliers was determined.

Results. The mean total AbC rate was 821.2 DOTs/1000 PDs or 4487.6 DOTs/1000 discharges. Model I explained 31% of the variability in AbC

measured in DOTs/1000 PDs while Model II explained 64% of the variability in AbC measured in DOTs/1000 discharges. The E/O ratios ranged from 0.76-1.44 while the O/E ratios ranged from 0.73-1.45. The comparison of the risk-adjustment methods revealed a very good agreement between the two regression models as well as between the two standardization methods whereas the agreement of Model II with either standardization method was moderate.

Conclusion. Standardization provides a viable alternative to regression for benchmarking hospital AbC rates. Direct standardization appears to be especially useful for benchmarking purposes since it allows the direct comparison of risk-adjusted rates.

Chapter I
Introduction

1.1 Brief Overview

The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines for developing antimicrobial stewardship programs (ASPs) recommend that hospitals measure their antimicrobial use and compare it, after risk-adjustment, with that of other institutions [1,2]. This process of interinstitutional comparison for the purpose of quality improvement is known as “benchmarking”. More specifically, interinstitutional comparison is known as “external benchmarking” while intrainstitutional comparison is known as “internal benchmarking”.

The need for hospitals to measure and monitor their antimicrobial use is becoming an increasingly pressing issue given the ever-increasing antimicrobial resistance rates. Antimicrobial use increases the rate by

which resistant microorganisms emerge by exerting selective pressure on these microorganisms [3,4]. Many hospitals have adopted ASPs as a means of overseeing the quality and quantity of their antimicrobial prescribing. In particular, ASPs strive to identify and minimize inappropriate antimicrobial therapy. A validated benchmarking model for antimicrobial use should be another useful tool for hospitals to assess their antimicrobial consumption as it will help them determine whether this consumption is consistent with their "risk" profile. Such benchmarks can work in tandem with ASPs to help guide and improve antimicrobial prescribing practices.

In the absence of standardized national antimicrobial use rates, hospitals often evaluate the performance of their ASPs by comparing their antimicrobial use internally, before and after the adoption of such programs. Such internal benchmarking, while undoubtedly useful, does not provide hospitals with a tool to compare their antimicrobial use and ASPs with their counterparts that set the standard in these areas. This makes setting target goals for these quality control measures an often obscure proposition. By comparing their risk-adjusted antimicrobial use with their peers, hospitals may be able to make a more informative assessment of their antimicrobial use and the effectiveness of their ASPs. However, the direct comparison of antimicrobial use between hospitals may be flawed due to differences in characteristics pertaining to the hospitals themselves as well as the patients attending them. Accordingly, in order for this comparison to be meaningful, it is necessary to take these differences between hospitals

into account by risk-adjusting their antimicrobial use before actually comparing it.

1.2 Study Rationale

There are no details in the previously mentioned IDSA/SHEA guidelines, and very little guidance elsewhere, on how to risk-adjust antimicrobial use within or across hospitals. Regression modeling has been the standard methodology employed to risk-adjust and compare antimicrobial use in hospitals [5-7] with indirect standardization recently emerging as a viable alternative [8,9]. However, direct standardization has not been previously used for this purpose. The current investigation will apply, compare and assess the usefulness of direct and indirect standardization in risk-adjusting antibacterial consumption (AbC) in hospitals. This investigation will also risk-adjust AbC in hospitals using regression modeling and will compare this strategy with the standardization procedures.

This study assumes that the variability in antimicrobial use can be modeled and predicted. While antimicrobial use is not an outcome from a clinical perspective, but rather a resource utilization measure, it can be modeled and benchmarked in a similar manner to clinical outcomes (e.g., infection rates). Differences in antimicrobial use between hospitals can be attributed to modifiable (e.g., effectiveness of ASPs) and non-modifiable factors (e.g., severity of illness (SOI) and type of hospital); and by having a tool that adjusts for the latter, hospitals can compare their antimicrobial

use with that of peer institutions knowing that they can focus their efforts on the modifiable factors when evaluating their antimicrobial use.

1.3 Specific Aims

The current study has the following specific aims:

1. Apply direct and indirect standardization procedures to risk-adjust AbC in hospitals.
2. Develop and validate regression models for risk-adjusting AbC in hospitals using two different AbC rates.
3. Compare the two standardization methods with one another and the two regression models with one another as well as with the standardization procedures with respect to their ranking of hospitals based on their risk-adjusted rates and their agreement in identifying outliers.
4. Apply direct and indirect standardization to risk-adjust and benchmark the components of AbC at the hospital level including the proportion of discharges receiving antibacterials and proxy measures for the length of therapy and the average number of administered antibacterials.
5. Compare interhospital AbC and its components within specific strata that represent patients with similar medical conditions.

Chapter II
Background

2.1 Background on Benchmarking

Benchmarking may be defined as the process by which an institution compares its services, products, or performance with those of its competitors or industry leaders; with the purpose of using this as a reference to identify best practices that can be transferred to its own organization [10,11].

Benchmarking was first introduced to the corporate world as a formal process by the Xerox Corporation in the 1980s as part of its revival plan after its market share began to plummet due to fierce competition from Japanese and US competitors [12]. The company closely studied the best practices within as well as outside its industry and was able to regain its competitive advantage by employing these practices to reduce the cost and

improve the quality of its products. By the mid-1990s, motivated by the Xerox success story, hundreds of companies around the globe adopted benchmarking and implemented it at their facilities. It was not too long before health care institutions followed suit and started employing benchmarking tools to quality control measures such as comparing staff satisfaction [13], improving energy efficiency [14], and determining the appropriate staffing level [15,16].

Benchmarking has also found applications in almost every medical specialty and for a variety of objectives. For instance, it has been used in cardiology to evaluate quality of care of patients following acute myocardial infarction [17] and to compare bypass surgery mortality rates [18]. In pulmonology, benchmarking has been used to determine best practices for managing asthma patients [19], to compare the efficiencies in the treatment of mechanically ventilated patients [20], and in psychiatry, to determine the effectiveness of psychotherapy in adult depression [21,22].

2.2 Benchmarking in Infectious Diseases

In the field of infectious diseases (ID), benchmarking has been used to compare infection rates [23,24] as well as antimicrobial use in both hospitals [5,6,8,9,25-27] and long-term care facilities [28]. In the context of comparing antimicrobial use between hospitals, benchmarking may be defined as the process of interhospital comparison of antimicrobial use using a risk-adjustment method that accounts for differences between

hospitals in patient-mix, hospital characteristics and other non-modifiable factors so that this comparison is as fair and meaningful as possible.

2.3 Measuring Antimicrobial Consumption

A key element in the process of benchmarking antimicrobial use is finding a valid, stable, and preferably universal measure for quantifying antimicrobial drug use which is sensitive to differences in antimicrobial use across hospitals and countries [29]. The most commonly used metric for measuring antimicrobial drug use and the one that is promoted by the World Health Organization (WHO) is the defined daily dose (DDD). Antibacterials for systemic use fall under the J01 category of the Anatomical Therapeutic Chemical (ATC) classification system which, along with the DDD assignment, is updated annually by the WHO Collaborating Center for Drugs Statistics Methodology (currently in its 15th edition) [30].

The DDD assignment is based on the assumed average daily maintenance dose for the main indication of the drug in adults. The number of DDDs of an antimicrobial agent is normalized, to account for differences in hospitals census, by dividing it by a measure of hospital occupancy (usually the number of total patient-days (PDs) or admissions) to allow the comparison of antimicrobial use between different hospitals [29]. However, a major limitation of using the DDD metric for comparing antimicrobial use between hospitals is the fact that it may not reflect the dose that is actually administered to patients. Several studies have demonstrated that using

DDDs to measure and benchmark AMC suffers from serious shortcomings including that differences in DDDs reflect not only differences in AMC but also differences in the formulary composition between hospitals [31-34]. These studies proposed using alternative metrics to measure antimicrobial use such as the recommended daily dose (RDD), prescribed daily dose (PDD) and days of therapy (DOTs). The RDD and PDD may be appropriate for internal benchmarking but not for the comparison of antimicrobial use between hospitals and countries as they have the same limitations as the DDD metric [29]. On the other hand, the DOTs metric is not compromised by some of these limitations since it is stable and not affected by changes in DDD or PDD over time or across countries. Accordingly, and as concluded by Polk et al. [32], it can be argued that the DOTs metric is superior to DDD for measuring and comparing antimicrobial use between hospitals and countries.

The DOT measure, however, has its own limitations. The DOT is insensitive to the dosage administered and it does not provide an accurate measurement of the duration of therapy [29]. One metric that does measure the duration of therapy and that has been used to measure antimicrobial use has been called “antibiotic days” [35] and “patient-days receiving antimicrobials” [36]. Recently, it has been also used to benchmark AbC in hospitals and has been called “length of therapy (LOT)” [9]. It represents the number of days a patient receives systemic antibacterial therapy irrespective of the number of different antibacterial agents, number of doses or dosage

administered. Obviously, LOT suffers from a number of limitations and probably should not be used as the sole measure of antimicrobial use. However, the information obtained from the LOT measure complements that obtained from DOT since they capture different aspects of antimicrobial use. Moreover, the DOT/LOT ratio may be regarded as a parameter that measures the average number of antibacterial agents administered, which provides yet another dimension that may be helpful in benchmarking antimicrobial use [29].

The debate surrounding the measurement of antimicrobial use is not confined to the numerator of the antimicrobial use rate. Several studies have also debated the denominator of the antimicrobial use rate [34,35,37,38]. The most commonly used measures in the denominator of antimicrobial use rates are the number of patient days and, to a lesser extent, the number of admissions. The total number of patient days is the product of the total number of admissions and the average LOS (also the sum of the individual LOS). Expressing antimicrobial use with the number of admissions in the denominator rather than number of patient days may provide a better correlation with antimicrobial resistance [37]. In addition, the two denominators were found to lead to different conclusions in two investigations of antibiotic use trends over time [34,38]. This discrepancy between the two denominators may extend to the interhospital comparison of antimicrobial use.

2.4 Severity of Illness and Case-mix Index

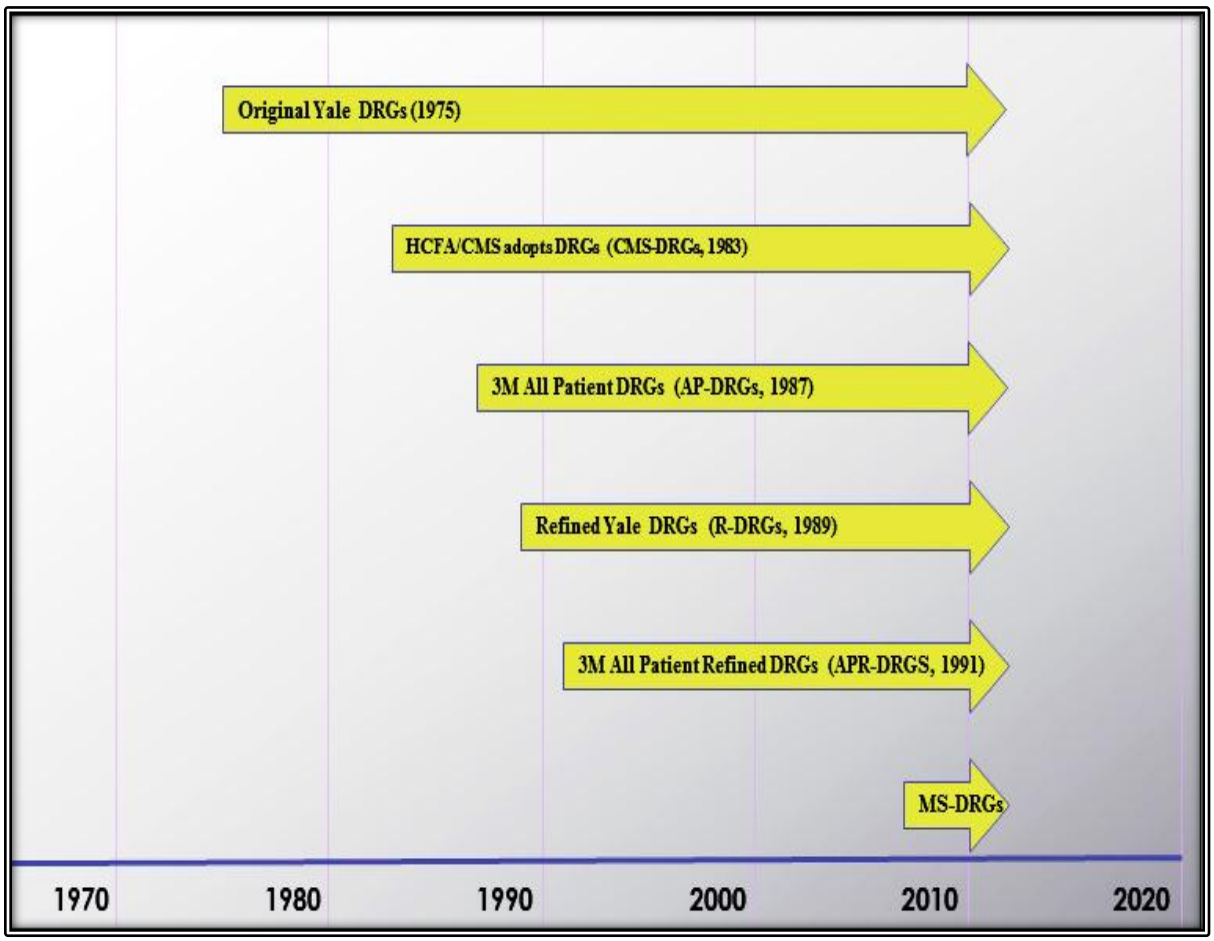
Hospitals often justify their high antimicrobial use by contending that they attend to a patient population with a high SOI [7]. Critically ill patients usually require an aggressive antimicrobial therapy approach to manage their infections. Such patients often receive multiple antimicrobial agents at higher doses and for longer durations compared to patients whose illnesses are less severe [29]. Thus, adjusting for SOI is imperative if valid conclusions are to be drawn from comparing antimicrobial use across hospitals.

Several scoring systems have been developed to classify patients according to their SOI, comorbidities and mortality risk [39-42]. However, these systems measure SOI at the patient level rather than the institutional level. One measure that is widely used as a surrogate marker of SOI at the institutional level is the case-mix index (CMI) [7]. The CMI is an economical surrogate marker that relates the average SOI of patients admitted to a particular hospital during a specific time frame to their resource utilization. It represents the average relative weight (RW) of diagnosis-related groups (DRGs) assigned to all inpatient cases in a hospital during a given time period [43]. The RW is a numerical figure assigned to each DRG reflecting the expected national average resource utilization of patients in that group relative to the national average resource utilization of all patients [44].

The development of the DRG classification system started in the 1960s by a research group at Yale University but its first widespread application was not until the late 1970s when the New Jersey State Department of Health used DRGs for hospital reimbursement [45]. In 1983, the Centers for Medicare and Medicaid Services (CMS; formerly the Health Care Financing Administration, HCFA) adopted an expanded and thoroughly revised version (CMS-DRGs) of the original DRGs as part of its inpatient prospective payment system (IPPS) which reimburses hospitals for providing inpatient care to Medicare beneficiaries [46]. However, it has been argued that the CMS-DRGs do not adequately adjust for SOI and this may lead to inequities in reimbursement especially for hospitals that treat sicker patients [47,48]. Moreover, this classification system was developed using data in which special patient populations such as neonates and the SOI in such populations. CMS addressed some of these limitations by introducing a substantially revised DRG classification system in 2007 known as the Medicare Severity DRG (MS-DRG) which is currently in its 29th version [44]. Each patient is assigned to one of over 700 MS-DRGs based on the principal and secondary diagnoses, gender, procedures performed, the presence of co-morbidity and/or complications and discharge status. While this revised version may outperform the CMS-DRG system by more accurately relating resource utilization of patients with their SOI, it still suffers from the same shortcoming of its predecessor in underrepresenting special patient populations.

Several proprietary DRG classification systems have been developed, of which the All Patient Refined DRG (APR-DRG) developed by 3M Health Information systems (Salt Lake City, Utah) is the most widely used [49]. The APR-DRG system was developed in 1990 (current version is 29) and has SOI as well as risk of mortality components for all patient populations. It expands the basic DRG structure by adding four SOI and risk of mortality subclasses to each DRG that are measured on an ordinal scale (1–4) representing, respectively, minor, moderate, major or extreme SOI or risk of mortality. The APR-DRG methodology has been validated in large databases and has been found to have the best ability (highest R^2) in predicting LOS for hip fracture [50] and pneumonia patients [51]. The history and evolution of DRGs are summarized in Figure 1.1.

The CMI has been found to be significantly correlated with AbC across various units of a university hospital as well as across different acute care hospitals in Switzerland [7]. Additionally, a study of general and tertiary care hospitals in Greece and Cyprus demonstrated the importance of adjusting for the CMI when comparing infection rates across hospitals [23]. However, these studies used international versions of DRGs to calculate the CMI which are likely to vary from MS-DRG and the APR-DRG based CMIs. It is not known whether CMIs calculated based on different DRG classification systems vary substantially in their usefulness for benchmarking antimicrobial use.



CMS; Centers for Medicare and Medicaid Services; HCFA, Health Care Financing Administration; MS-DRGs, Medicare Severity-Diagnosis Related Groups

Figure 2.1 History and evolution of Diagnosis Related Groups (DRGs)

2.5 Risk-adjustment and Patient Mix

As previously mentioned, the comparison of crude antimicrobial use rates between hospitals may lead to erroneous conclusions. Differences in antimicrobial use between hospitals may stem from differences in hospital characteristics and in the characteristics and risk factors of patients attending them. Risk adjustment is a statistical process used to remove or minimize the effect of confounding factors that differ among comparison groups.

Hospital characteristics and patient mix are two important confounding factors that should be accounted for when comparing antimicrobial use between hospitals. Patient mix refers to the distribution of patients' demographics, risk factors, and diagnoses. Certain patient subgroups (e.g., Surgical and febrile neutropenic patients) are more likely to receive prophylactic or empiric antimicrobial therapy than others (e.g., psychiatry patients) [52]. Such patients are also at a higher risk of acquiring healthcare-associated infections (HAIs) and, consequently, also more likely to receive definitive antimicrobial therapy.

In addition to differences in patient-mix, differences in AMC between hospitals may be associated with differences in hospital characteristics. Hospital characteristics such as the size, location, teaching status, as well as the quality of care and reputation of hospitals have a direct influence on the patient mix of these hospitals. Hospitals offering comprehensive and

advanced services require expensive medical equipment and specialized personnel, and tend to attract patients with severe conditions and complex clinical profiles. However, in addition to their influence on patient mix, hospital characteristics may also influence other determinants of AMC such as antimicrobial resistance rates. Accordingly, it may be important to account for both differences in hospitals characteristics and differences in patient mix in order for the interhospital comparison of AMC to be more fair and accurate. It is important to mention that benchmarking involves accounting for factors that are beyond the control of hospitals (non-modifiable factors) and should not include factors related to the quality of service provided by these hospitals (modifiable factors). Patient mix and hospital characteristics are such non-modifiable factors.

Regression modeling is the most commonly used statistical method for risk-adjustment [53-55]. Multivariable regression models such as linear and logistic regression have found wide application in risk-adjustment in the medical literature and have been previously used to benchmark antimicrobial use [5,6,27]. The procedure of applying multivariable regression to benchmarking outcomes in hospitals requires -as a first step- determining the important risk-adjustment factors for the outcome of interest and using these factors to build the model. The next step involves using the estimated model to calculate –for each hospital- expected (predicted) values of the outcome that are risk-adjusted for the factors identified in the first step. The third step is to calculate the residuals

(differences between observed and expected values) and use them to determine the hospitals that have higher than expected AMC and the ones that have lower than expected AMC. The final step is to determine potential outliers and to rank the hospitals according to their performance.

Another widely used statistical method for risk-adjustment is "standardization (of rates)". It is based on the stratification of the confounding variable into sub-groups and then calculating a weighted average of the stratum-specific (sub-group) rates. Standardization of event rates has been used to compare hospital performance in various medical specialties [56-58]; and recently, to risk-adjust antimicrobial use in hospitals [8,9].

The two main standardization procedures are direct and indirect standardization. Direct standardization applies the stratum specific rates (e.g., incidence rate, mortality rate, DOTs/1000 PDs, etc.) of each study population (e.g., study hospital) to the number of cases (or number of person-years, PDs, etc.) in the corresponding stratum in the reference (standard) population. An expected number of cases (or deaths, DOTs, etc.) is generated for each stratum. These stratum specific numbers are added to yield the total expected number which is used in the numerator of the directly standardized rate (DSR). The denominator is the total number of individuals (or total number of person-years, total number of PDs) in the reference population. DSRs can then be compared for different populations using relative risks (RR) or attributable risk (AR) differences. In indirect

standardization, the roles of the study population and the reference population are reversed. That is, the stratum specific rates are now provided by the reference population while stratum sizes of the study population are used as weights. The rest of the procedure is similar to that of direct standardization except that the summary statistic that is usually reported in indirect standardization is the standardized mortality ratio (SMR) or the standardized incidence ratio (SIR).

The main advantage of DSRs is that they can be directly compared across different populations or hospitals whereas indirectly standardized rates cannot (except in limited cases when certain conditions are met) [59]. Therefore, direct standardization may be the more appealing of the two procedures in benchmarking outcomes and quality of care across healthcare institutions.

The application of direct (and indirect) standardization to benchmarking antimicrobial use in hospitals entails stratifying antimicrobial use by meaningful categories (sub-groups) of the risk-adjustment factor (confounder). Accordingly, standardization of rates methods may be employed to risk-adjust antimicrobial use in hospitals for patient mix by stratifying antimicrobial use by some criteria that represent patient mix such as patient care areas or primary diagnosis (DRGs).

2.6 The Role of Benchmarking In Identifying Inappropriate Antimicrobial Therapy

The majority of investigations that studied the consequences of inappropriate antimicrobial therapy focused on the impact of inappropriate selection of initial therapy or the delay in the initiation of appropriate therapy on patient outcomes [60-64]. These studies concluded that, in addition to having detrimental impact on patient outcomes and mortality, inappropriate therapy may also increase the rate by which antimicrobial resistance emerges. In addition to improper selection of initial therapy and the delay in initiation of appropriate therapy, inappropriate antimicrobial therapy includes situations where antimicrobial therapy is administered without being indicated. Inappropriate antimicrobial therapy also encompasses, among others, situations where the dose, dosage form, duration of therapy, as well as route and frequency of administration are less than optimal.

According to the Centers for Disease Control and Prevention (CDC), 25%-45% of antibiotic use in hospitals is inappropriate [65]; while different studies in the United States and the United Kingdom indicated that this figure may be as high as 50% [66-70]. The concept behind risk-adjusting and benchmarking healthcare outcomes is to adjust for differences in patient mix and other non-modifiable factors so that the remaining

variability between institutions may be attributed to differences in the quality of care. This concept can be applied to benchmarking antimicrobial use such that differences between risk-adjusted antimicrobial use rates in hospitals may be attributed to differences in inappropriate antimicrobial therapy. From a benchmarking perspective, inappropriate therapy may be expressed in the components of antimicrobial use rates including LOT, proportion of patients receiving therapy and/or patients receiving combination therapy. The extent of inappropriate therapy may be considered as a marker for the quality and effectiveness of ASPs and, perhaps to a lesser extent, infection control programs.

While it is fairly easy to measure LOT and the proportion of patients receiving combination therapy, measuring inappropriate antimicrobial therapy is a more complicated and laborious undertaking that requires access to patient-level data and drug utilization reviews (DURs). However, the goal of benchmarking antimicrobial use is not necessarily to accurately quantify inappropriate antimicrobial therapy, but rather to entertain the possibility that differences in adjusted antimicrobial use rates between hospitals may be attributed-at least partially-to differences in inappropriate antimicrobial therapy rates.

A validated benchmarking model for antimicrobial use will serve as a tool for identifying hospitals with extremes in antimicrobial usage. It will allow hospitals with high or average antimicrobial use to compare their

consumption rates with those of hospitals whose consumption is relatively low, after adjusting for factors that predict use volume. This will hopefully motivate the former hospitals to scrutinize their antimicrobial therapy and perform DURs in order to facilitate the identification of areas of deficiency in their antimicrobial prescribing and management. These hospitals can then develop a homegrown strategic plan or adopt a "battle-tested" paradigm from one of their top performing peers to help optimize their antimicrobial therapy and curtail their inappropriate therapy.

Finally, hospitals could conduct internal benchmarking to compare their antimicrobial use before and after the adoption of either the local or the imported remedial program. This will serve the purpose of determining whether the antimicrobial use target has been met, needs to be reset or whether the program needs to be modified. The amount of reduction in total and inappropriate antimicrobial use will ultimately depend on – assuming no change in patient mix and severity of illness- the effectiveness of the newly adopted or modified strategy, how well a hospital implements and adheres to the strategy and the hospital's baseline consumption rate.

2.7 Effectiveness of Strategies Used to Reduce Inappropriate Antimicrobial Therapy

Most of the literature on the effectiveness of the different strategies to minimize inappropriate antimicrobial therapy comes from single-center studies. A French study reported that a single 1-hour educational session

delivered by an ID physician reduced the use of inappropriate empirical antibiotic therapy in patients with positive urine cultures by 17% compared to the control group [71]. Another study conducted in a single tertiary care teaching hospital in the United States reported a 20.6% decrease in inappropriate vancomycin prescriptions after implementing a persuasive strategy (e.g., education, reminders, etc.) to control vancomycin prescriptions [72]. Another study in a teaching hospital in the United States reported a 17% decrease (from 53% to 36%) in inappropriate dosing of cefazolin after employing a persuasive strategy to control cefazolin prescribing [73].

While persuasive strategies may only result in modest reductions in inappropriate antimicrobial therapy, restrictive strategies (e.g., formulary restriction, pre-authorization of prescriptions and automatic stop orders) may have a greater impact [74]. Having said that, even a reduction as small as 5% in inappropriate antimicrobial use may be substantial if coupled with a significant improvement in clinical or operational performance (e.g., mortality rates and length of stay), economical performance (e.g., direct and indirect cost savings resulting from reduced antimicrobial use), or resistance rates.

The importance of keeping antimicrobial use in check cannot be overstated given the well-documented association between antimicrobial use and antimicrobial resistance [75-79]. Antimicrobial resistance is an

inevitable consequence of the selection pressure exerted by the use of antimicrobials. Thus, resistant microorganisms will evolve even with the most prudent use of antimicrobials. However, inappropriate antimicrobial use may increase the rate by which resistant organisms emerge and; consequently, the rate by which these antimicrobials become obsolete. This is especially alarming given the dearth of novel antimicrobials in the drug development pipeline [80,81]. Accordingly, it is crucial to use the current antimicrobials as wisely as possible in order to preserve their effectiveness for as long as possible.

It is difficult to discern how much reduction in inappropriate antimicrobial use is needed to have a significant reduction (if any at all) in resistance rates since the literature on this issue is quite sparse. The vast majority of studies that investigated the effect of inappropriate antimicrobial therapy focused on its detrimental impact on mortality rates, LOS, and cost [61-64]. The few studies that explored the relationship between inappropriate antimicrobial therapy and antimicrobial resistance reported a significance decrease in ceftazidime-resistant *Klebsiella* and in infections caused by resistant *Enterobacteriaceae* when measures enforcing appropriate antimicrobial therapy were employed [82,83].

2.8 Literature on Benchmarking Antimicrobial Consumption

Most of the data on antimicrobial use and its variability between different hospitals or countries comes from antimicrobial surveillance programs that

usually collect such data with that on infection rates in order to highlight the association between antimicrobial use and antimicrobial resistance [84,85]. Such surveillance programs usually report crude antimicrobial use rates that are not adjusted for patient mix, SOI, and other important predictors of antimicrobial use because benchmarking was not their purpose. One surveillance program that did benchmark AbC is the CDC's Intensive Care Antimicrobial Resistance Epidemiology (ICARE) Project [86,87]. The project pooled AbC in all study hospitals over the entire study period and subsequently risk-adjusted this aggregate AbC by stratifying hospitals according to patient areas where patient mix is likely to be relatively homogenous such as medical, surgical, and cardiothoracic intensive care units (ICUs). Study hospitals were then provided with these area-specific benchmarks to compare with their local AbC in the corresponding patient areas.

Project ICARE was one of the earliest efforts to benchmark AbC in hospitals and whereas it used stratification as the risk-adjustment method, subsequent benchmarking investigation used univariable [7] and multivariable [5,6,27] regression models to risk-adjust AbC in hospitals. More recently, standardization (of rates) was used to risk-adjust AbC in hospitals [8,9]. I will first review the studies that used regression as a strategy for benchmarking hospital AbC and will then review the investigations that used standardization for this purpose.

Investigations that Used Regression Modeling to Benchmark Antibacterial Consumption

The first study I will review used univariable weighted linear regression to examine the association between AbC (measured in DDD/100 bed-days and DDD/100 admissions) and the CMI in 18 departments at the University Hospital Zurich, a tertiary care teaching hospital, as well as in 13 acute care hospitals including the aforementioned tertiary care hospital, 2 secondary care and 10 primary care hospitals in the Canton of Zurich in Switzerland [7]. The number of bed-days of each department or hospital was used as a weighing factor. The investigators reported a significant correlation between the CMI and AbC when measured in DDD/100 bed-days as well as when measured in DDD/100 admissions, respectively, in the different university hospital departments (R^2 = 0.57, p-value = 0.0002 and R^2 = 0.48, p-value = 0.0008) and also across the different acute care hospitals (R^2 = 0.46, p-value = 0.0065 and R^2 = 0.85, p-value < 0.0001), respectively.

The other 3 investigations that used regression to benchmark AbC used multivariable regression models and are summarized in Table 2.1. The study by Amadeo et al. developed regression models to explain the variability in AbC in 34 public non-teaching and 43 private hospital in southwestern France [5]. The “best” model for public hospitals explained 84% of the variability in AbC measured in DDD/1000 PDs using the

existence of an ID consultant and the proportion of PDs in medical and surgical wards and ICUs as predictor variables. The model fit was so good; however, that none of the hospitals fell outside the 90% prediction interval. For private hospitals, DDD/100 admissions was the "preferred" measure and the fitted model was able to explain 68% of the variability in AbC using the existence of an ID consultant, LOS, the proportion of PDs in the medical wards and the proportion of PDs in surgery as predictor variables. The variable "existence of ID consultant" was not statistically significant in either model but was forced into the models because the investigators deemed it to be an important factor in controlling AbC.

The study by MacDougall and Polk identified hospital size, the number of ICU days, surgical volume, and the number of cases of bacteremia, pneumonia and urinary tract infection (UTI) as predictors of total AbC measured in DOTs/1000 PDs in a sample of US hospitals that was primarily composed of non-teaching community hospitals [6]. The sample of 130 hospitals was randomly split into 2 equally sized datasets; a training set to fit the model and derive the prediction equation, and a validation set to derive the predicted values and prediction intervals. The fitted model was only able to explain 31% of the variability in AbC . Nevertheless, both low and high outlier hospitals were identifiable in this study.

The last study that used regression as a strategy to benchmark AbC was based in Germany [27]. Data including AbC over a 2-year period (2001-

2002) were retrieved from 2 different network databases (cohorts) composed of 92 ICUs representing 64 hospitals (58 non-teaching and 6 teaching). AbC, measured in both DDD/100 PDs and RDD/100 PDs, was dichotomized at the 75% percentile and entered as a binary outcome in a logistic regression model while potential predictor variables included ICU type (surgical, medical, interdisciplinary), affiliation to a university hospital (yes, no), hospital bed size (< 400 beds, 400-799 beds, > 800 beds) and cohort type. Separate models were fit for all ICUs and for non-teaching ICUs only. The findings of the different models are summarized in Table 2.1. The investigators concluded that "in order to compare the use of antibiotics between ICU cohorts and to assess trends over time, data adjustment is required for hospital affiliation and size".

Investigations that Used Standardization to Benchmark Antibiotic Use

The two studies that employed standardization to benchmark AbC thus far used the indirect standardization procedure. Polk and colleagues stratified adult AbC (measured as DOTs/1000 PDs and LOT/1000 PDs) in 70 US academic medical centers during 2009 into 35 CSLs. The assignment of patients to CSLs was based on the similarity of their clinical conditions as determined by their MS-DRG assignment. The investigators applied indirect standardization to derive expected AbC rates and the observed-to-expected (O/E) ratios. The reported O/E ratios ranged from 0.73 to 1.44 for the DOTs/1000 PDs measure. The study also determined the CSL-specific O/E

ratios and benchmarked the CSL-specific components of AbC including the proportion of discharges receiving antibiotic therapy, LOT/discharge and DOTs/LOT ratio. According to the investigators, “Perhaps the greatest advantage of this method is that the reasons for the high O/E ratios in each CSL can be identified and also benchmarked against all 70 hospitals” [29].

The second study used a combination of regression modeling and indirect standardization to risk-adjust AbC in 30 acute care hospitals in Finland during a 7-day prevalence study in 2005 [8]. AbC was measured during the study day and the 6 days preceding it and was expressed as antibiotic use-days/100 PDs. Predicted AbC was determined for each individual based upon a regression model that adjusted for several risk factors of antibiotic use and the predicted values were aggregated to determine the mean predicted AbC for each hospital. The indirectly standardized ratios were calculated by dividing observed use by predicted use in each hospital. Finally, risk-adjusted antibiotic use (indirectly standardized rates) was determined by multiplying the indirectly standardized ratio by the observed AbC in the entire study population. The investigators compared observed AbC ranks to risk-adjusted ranks and found that the two ranked hospitals differently in 25 hospitals (83%). They concluded that “Case-mix adjustment may be a useful tool for benchmarking hospital antibiotic use”.

This review of the literature pertaining to benchmarking antimicrobial use in hospitals reveals marked variability in the type and size of compared hospitals, antimicrobial agents included, SOI measure used, explanatory variables considered and the metric used to measure antimicrobial use. This severely limits the comparability of these investigations and the ability to draw conclusions about the generalizability of the various antimicrobial use benchmarking models.

Teaching hospitals may be systematically different from their non-teaching counterparts and the type of patients attending these hospitals may differ as well. Such differences are not always measurable or known but may be important determinants of antimicrobial use. Moreover, the vast majority of studies that benchmarked or compared antimicrobial use in the hospital setting are based in European countries that differ from the US in their healthcare systems and in some of the elements that may drive antimicrobial use. Countries differ in their antimicrobial therapy and microbiology laboratory guidelines, government sponsored healthcare insurance plans, healthcare awareness campaigns, approved antimicrobial agents, physicians' training, endemic diseases, and prescribing practices driven by patients' culture and expectations as well as by advertising and aggressive marketing strategies. Therefore, it is unlikely that a benchmarking model for antimicrobial use developed in one country can be adopted by another without alteration.

Table 2.1 A Summary of Investigations that Employed Multivariable Regression Models to Benchmark or Compare Antimicrobial Use Across Hospitals or Hospital Units

Study Authors, year and location	No. and type(s) of hospitals	Study period	Antimicro-bials included	Antimicrobial use rate	Potential predictors of antimicrobial use identified in the multivariable model	Adjusted R^2
MacDougall and Polk, 2008 [6] United States	130 hospitals 115 community, 15 teaching	Aug 2002-Jul 2003	All systemic antibacterial drugs (n=87)	Mean (SD): 789.8 DOTs/1000 PDs (123.5)	No. of beds, no. of ICU days, surgical volume, and no. of cases of pneumonia, UTI, and bacteremia	0.31
Amadeo et al., 2009 [4] France	77 hospitals 34 public (non-teaching), 43 private	2005 calendar year	Group J01 of ATC classification system (2006 version)	Median (range): DDD/1000 PDs and DDD/100 ADMS **Public**, 395 (196-737) and 341 (180-792) **Private**, 422 (113-117) and 212 (38-510)	**Public** (DDD/1000 PDs): proportion of PDs in surgery, ICU, and medical wards **Private** (DDD/100 ADMS): LOS, proportion of PDs in surgery and medical wards	**Public,** 0.84 **Private**, 0.68
De With et al., 2006 [27] Germany	Two cohorts of ICUs (n=92) representing 64 hospitals (6 teaching and 58 non-teaching)	Two calendar years 2001-2002	Major antibiotic drug classes	Median (IQR: DDD/100 PDs and RDD/100 PDs **Teaching**, 136.0 (99.1-180.7) and 84.0 (66.5-108.4) **Non-teaching**, 110.3 (88.6-128.6) and 61.6 (47.5-76.7)	**All ICUs** DDD/100 PDs: hospital affiliation RDD/100 PDs: hospital size **Non-teaching hospital ICUs** DDD/100 PDs: none RDD/100 PDs: ICU type	Not applicable, antimicrobial use was dichotomized and a logistic regression was fitted

ADMS: admissions, ATC: Anatomical Therapeutic Chemical, DDD: defined daily dose, DOTs: days of therapy, ICU: intensive care unit, IQR: interquartile range, LOS: length of stay, PDs: patient-days, RDD: recommended daily dose, SD: standard deviation, UTI: urinary tract infection

Chapter III
Development and Validation of the Multivariable Linear Regression Models

3.1 Methods

3.1.1 Study Design and Data Source

This study is a retrospective, cross-sectional, hospital-wide analysis of total antibacterial drug consumption (AbC) in a sample of US academic medical centers. Data on systemic AbC in adult (> 18 years) hospitalized patients for the 2009 calendar year was obtained from the University HealthSystem Consortium (UHC); an alliance of 107 academic medical centers and 221 of their affiliated hospitals representing all major geographical regions in the United States and 90% of the nation's non-profit academic medical centers. A subset of the UHC member hospitals participate in the Clinical Resource Manager (CRM) database which collects from its participants data such as diagnosis, patient outcomes, drug use, and demographics in addition to data on operational and financial performance.

Further details on how the CRM database extracts drug use and other data was described in a publication that investigated trends in adult AbC within UHC [88]. The CRM database offers its members access to risk-adjusted comparative data and benchmarking tools that enables them to compare their clinical and operational performance with that of other member hospitals. The UHC database has been previously used to benchmark surgeon satisfaction [13], mechanical ventilation services [20], and the quality of palliative care services [89]. However, antimicrobial benchmarking is not currently available within the UHC system, nor any other multi-hospital system of which I am are aware. This makes this database particularly suitable for developing benchmarking models for AbC in hospitals which is the main objective of the current study. This study has Institutional Review Board of Virginia Commonwealth University approval.

3.1.2 Outcome Variable

The total systemic AbC rate in adults is the primary outcome variable in the multivariable linear regression (MLR) models and is expressed as the number of DOTs per one thousand patient-days (DOTs/1000 PDs) in the first model (Model I) and as the number of DOTs per one thousand discharges (DOTs/1000 discharges) in the second model (Model II). The DOTs for 52 commonly used systemic antibacterial preparations (Table A1 in Appendix) were summed up to give the total number of DOTs for each hospital which was divided by either the number of PDs or the number of

discharges and multiplied by 1000 to yield the DOTs/1000 PDs and DOTs/1000 discharges rates, respectively. All data were aggregated at the hospital level and patient-level data were not identifiable in this study.

3.1.3 Predictor Variables

The drivers of antimicrobial drug use have not been fully explored and may vary by hospital type and country. Therefore, this study does not have a primary independent variable since it is of interest to identify all predictors of antimicrobial drug use in US teaching hospitals.

The CRM database obtains the numbers of various infections using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes reported by participating hospitals (Table A2 in Appendix). The rate of total infections was calculated from the ICD-9-CM based numbers of urinary tract infections (UTI), bloodstream infections (BSI), and pneumonias. An APR-DRG based CMI was also extracted from the CRM database. Another SOI measure extracted from the database was the percent of discharges in the combined major and extreme subclasses of the APR-DRG SOI classification. Other potential predictor variables provided by the database include bed size, geographic location, and the number of different types of surgeries and transplants. Again, the latter were summed up and normalized to yield a measure for the total surgery rate and another for the total transplant rate. The infection, surgery, and transplant rates were expressed as the number of events per 1000 discharges.

3.1.4 Statistical Analysis

The mean and the standard deviation (SD) were used to describe the outcome variable and continuous predictor variables if normality was warranted. If the normality assumption was markedly violated, then the median and inter-quartile range (IQR) were used to describe these variables. Categorical variables were summarized using counts and proportions. All statistical analysis was performed using JMP (version 8; SAS Institute, Cary, NC) and SAS (version 9.1.3; SAS Institute, Cary, NC) software.

All potential predictor variables listed under subsection 3.1.3 were separately fitted against each of the two outcomes (DOTs/1000 PDs and DOTs/1000 discharges) to screen candidate variables that are likely to be useful in explaining the variability in AbC in the two MLR models. An MLR approach was used to build the models using those variables that were significant at the $\alpha = 0.30$ significance level in the bivariate analyses. The *all possible regressions procedure* was used in conjunction with the sequential variable selection procedures (forward selection, backward elimination, and stepwise regression) to select the "best" model for each outcome measure from the subset of potential predictor variables screened in the bivariate analyses. The significance level for the entry and retention of variables in the model using the stepwise regression procedure was set to $\alpha = 0.20$ and $\alpha = 0.10$, respectively. The former significance level was also used for entry of variables in the forward selection procedure while the latter significance level was also used as the criteria for retaining variables in the backward

elimination procedure. The all possible regressions procedure uses all k potential variables to fit $(2^k - 1)$ possible subset models. The models are then ranked based on various selection criteria. The selection criteria considered were the R^2, adjusted R^2 (R^2_{ADJ}), mean square error (MSE), Mallows' C_p, the **P**redicted **R**esidual **E**rror **S**um of **S**quares (PRESS) statistic, and the corrected Akaike information criterion (AICc). These statistics and acronyms, as well as the others mentioned in this subsection, are defined and discussed in more details in section 3.2.

The assumptions of linear regression including linearity, independence, homoscedasticity of residuals and normality were checked for the final models. Consideration to a Poisson regression model, with the log of the denominator of the response variable as the offset, was given depending on whether these assumptions were violated or not. The final model was checked for multicollinearity problems using the variance inflation factors (VIFs). If multicollinearity was identified, then the least significant of the multicollinear variables would be taken out of the model. If this compromised the model's performance substantially, a procedure that combats multicollinearity such as Ridge regression was considered.

The R-student statistic was used to identify outliers at $\alpha = 0.05$ and $\alpha = 0.10$. A hospital was considered to be a high outlier if its R-student value exceeded the upper critical value of the t-distribution at the given significance level, a low outlier if its R-student value was less than the lower

critical value of the t-distribution, and a non-outlier if its R-student value fell between the foregoing upper and lower critical values. Influence diagnostics were checked to determine if any hospitals had an undue influence on the models' performance. DFFITS were used to check if any hospitals had a high influence on the fit of the regression model while DFBETAS were used to check whether any hospitals had an impact on the parameter estimates. COVRATIO were used to determine which hospitals, if any, had a positive or a negative impact on the model.

The final models were validated using both internal and external validation methods. Internal validation was carried out using the "leave-one-out cross validation" (LOOCV) method. In this procedure, an observation (e.g., the first observation) is removed from the dataset and the remaining n-1 observations are used to fit the model. The predicted value of the excluded observation is calculated from the prediction equation of the model from which it was excluded (i.e., the model fitted with n-1 observations). The difference between this "leave-one-out" predicted value and the observed value is known as the "PRESS residual". The excluded observation is then reinserted into the model and the next observation (e.g., the second observation) is removed from the model and so on. This procedure is repeated in a sequential manner for all n observations and all n PRESS residuals are calculated. The sum of squares of all n PRESS residuals is nothing but the aforementioned PRESS statistic. In addition to being a model selection criterion, the PRESS statistic is also useful for model

validation purposes. For the latter purpose, the PRESS statistic is usually expressed as the predicted R^2 (R^2_{PRED}) since it allows direct comparison with the adjusted R^2. The two statistics should be in "reasonable agreement". More specifically, the predicted R^2 should be within 0.2 of the adjusted R^2 for the model to be valid (not overfit) [90].

For the external validation method, the validation set consisted of a subset of the hospitals used in the calibration (i.e., model fitting) set but the data used was from 2008 instead of 2009. The prediction equations of Model I and Model II were applied to the validation set to obtain the respective predicted values. These were plotted against the corresponding observed values from the validation set to calculate the "validation" adjusted R^2 which were compared to the corresponding "calibration" adjusted R^2 of Model I and Model II.

3.2 Results

3.2.1 Descriptive Statistics

Hospital-wide Demographics

Seventy UHC member hospitals provided their AbC data in adults for 2009. All hospitals provided data for all four quarters of 2009 with the exception of Hospital #44 and Hospital #70, which only provided three quarters worth of data. All major geographic regions (New England, Mid-Atlantic, Southeastern, Midwestern, Mid-continent, and Western) were well represented with the number of hospitals in each region ranging from 7 (10%) in New England to 16 (23%) in the Midwestern region. Out of the 67 hospitals whose bed size was known, a total of 56 hospitals (84%) had a bed size between 200 and 800; while the average bed size was 561.

A total of 1,781,020 discharges (mean= 25,443, SD= 10,500) contributed an estimated 9,786,743 PDs (mean= 139,811, SD= 59,886) yielding an average LOS of 5.5 days (SD= 0.57). An estimated 55.7% (range= 47.2%-81.1%) of discharged patients were females with the average age being 52.5 years (SD= 4.7). A more comprehensive summary of the demographic and clinical characteristics of this sample of hospitals is presented in Table 3.1.

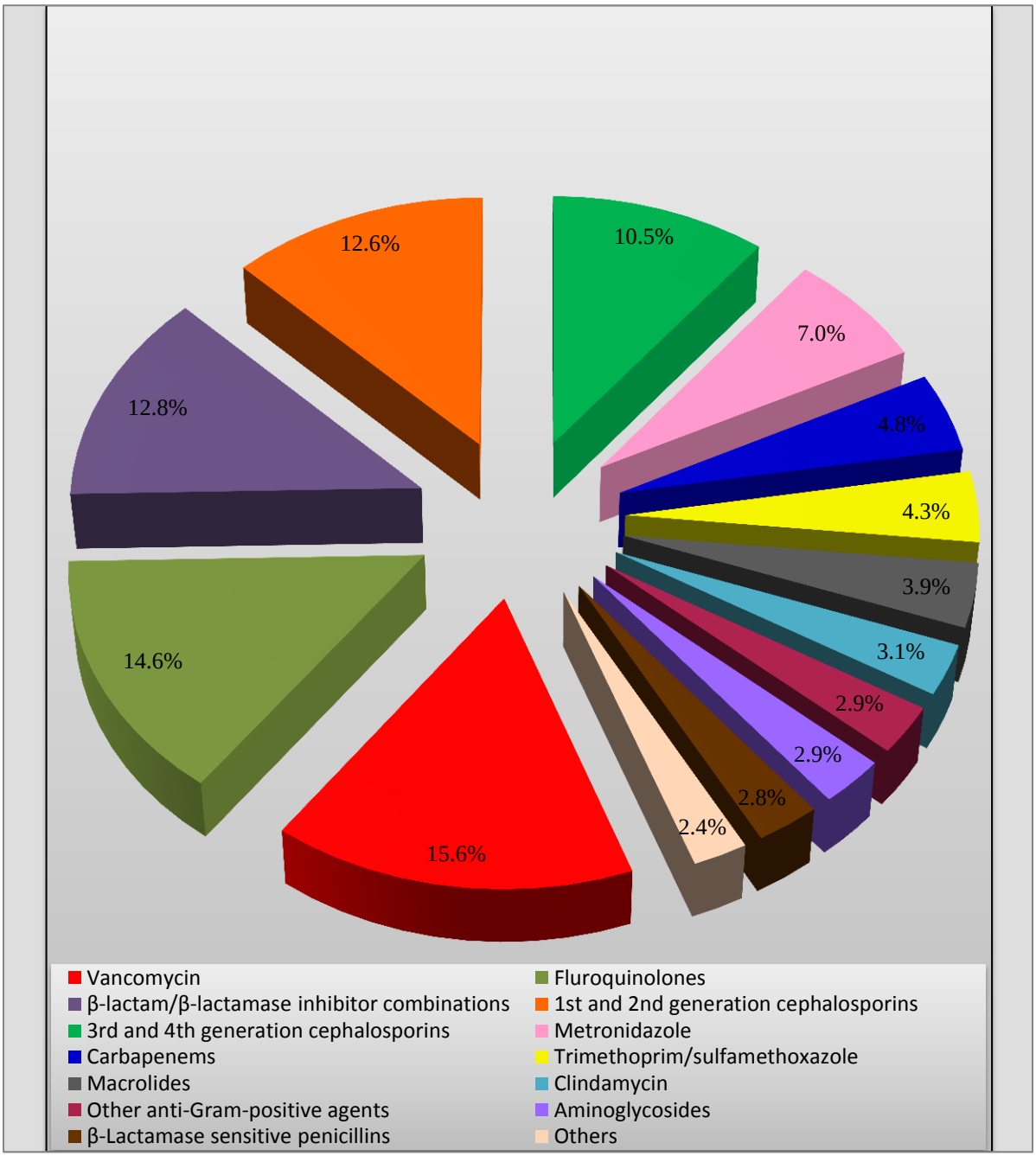
Table 3.1 Demographic and Clinical Characteristics of 70 US Academic Medical Centers in 2009

Characteristic	n	Percent
Geographic region		
New England	7	10.0
Mid-Atlantic	13	18.6
Southeastern	11	15.7
Midwestern	16	22.9
Mid-Continent	14	20.0
Western	9	12.9
Bed size category (N= 67)		
<200	1	1.5
200-399	18	26.9
400-599	20	29.9
600-799	18	26.9
800-999	9	13.4
≥1000	1	1.5
Characteristic	**Mean (SD)**	**Range**
Bed size (N= 67)	560.5 (204.3)	185-1156
Age, years	52.5 (4.7)	40-65
Discharges	25443 (10500)	4104-54204
Total patient-days	139811 (59886)	14373-299505
Length of stay, days	5.5 (0.57)	3.5-6.9
Duration of total antibacterial therapy, days	4.7 (0.62)	2.7-6.3
Case mix index	1.68 (0.20)	1.12-2.07
Surgical procedures per 1000 discharges	388 (69)	149-566
Diagnoses per 1000 discharges		
Bloodstream infections	55 (14)	14-88
Pneumonias	63 (14)	20-94
Urinary tract infections	85 (16)	29-119
	Median (IQR)	**Range**
Bone marrow transplants	2.3 (0-4.1)	0-15.3
Solid organ transplants	5.0 (2.3-8.6)	0-28.1
APR-DRG SOI subclass, no. of patients per 1000 discharges		
Minor	261 (238-299)	176-425
Moderate	376 (362-391)	321-496
Major	270 (250-286)	134-400
Extreme	98 (85-116)	9-146

APR- DRG, All Patient Refined Diagnosis Related Groups; SOI, Severity of Illness

Hospital-wide Aggregated Antibacterial Drug Consumption

On average, 63.5% (range= 49.5%-76.1%) of discharged patients received at least one dose of an antibacterial agent. About 44.3% of these patients received a single antibacterial agent, 26.7% received two antibacterial agents, and 29% received three or more antibacterial agents. The mean total AbC rate was 821.2 DOTs/1000 PDs (SD= 108.1, range= 560.8-1104.1) or 4487.6 DOTs/1000 discharges (SD= 859.2, range= 2521.7-7579.5), while the average LOT for total antibacterial drug therapy was 4.7 days (SD= 0.62). Figure 3.1 and Table 3.2 summarize AbC by antibacterial drug class. Glycopeptides -represented by vancomycin as the sole agent- were the most widely used class and accounted for 15.6% of total AbC. They were followed by fluoroquinolones (14.6%), β-lactam/β-lactamase inhibitor combinations (12.8%), 1st and 2nd generation cephalosporins (12.6%), and 3rd and 4th generation cephalosporins (10.5%). Broad spectrum antibacterial drugs (aminoglycosides, fluoroquinolones, third and fourth-generation cephalosporins, carbapenems, and β-lactam/β-lactamase inhibitor combinations) contributed a mean of 374.2 DOTs/1000 PDs or 2050 DOTs/1000 discharges (45.6%) to the total AbC rate.



Others, tetracyclines, antistaphylococcal penicillins, nitrofurantoin, and sulfadiazine

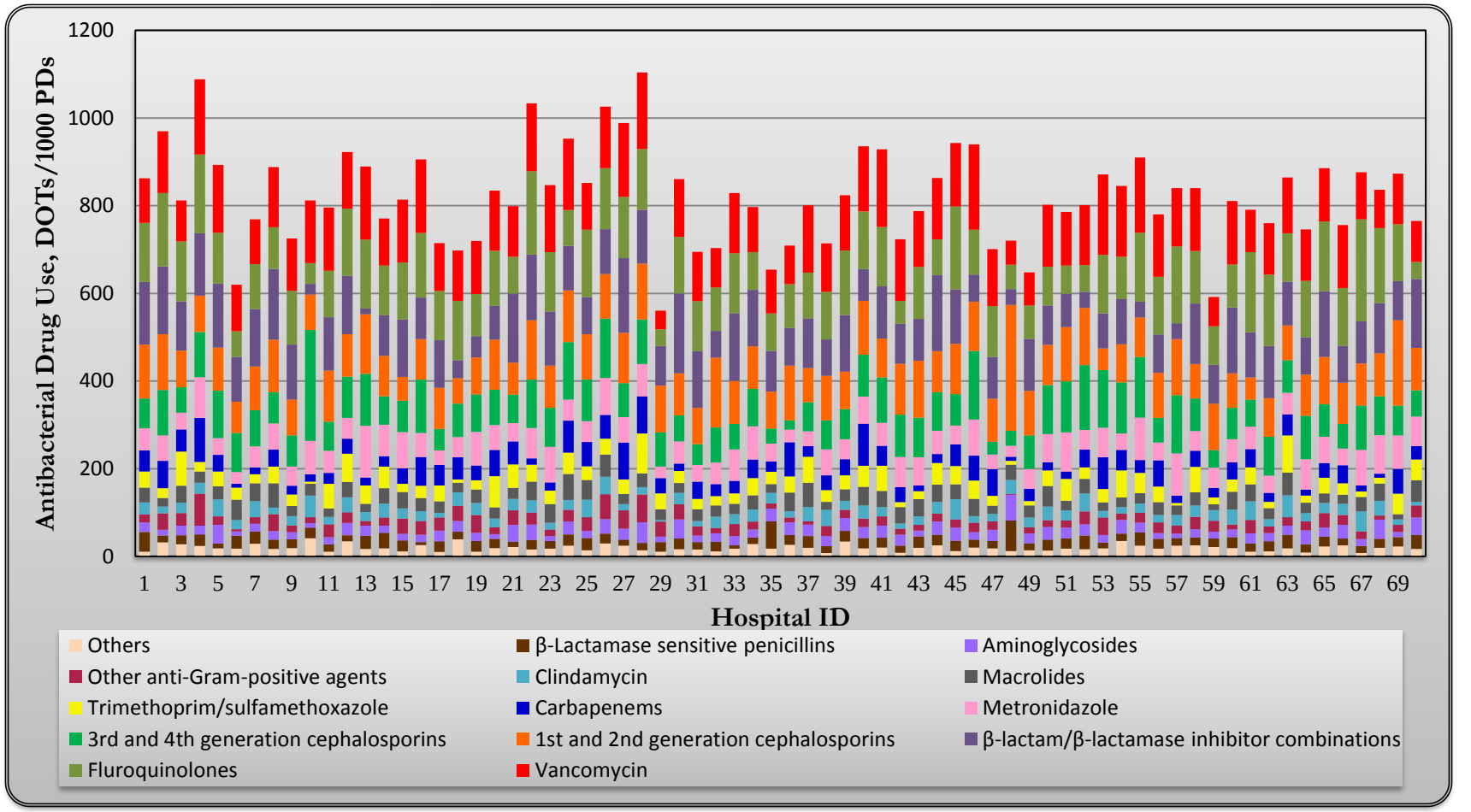
Figure 3.1 Breakdown of total antibacterial drug consumption at 70 US academic medical centers in 2009 by antibacterial drug class. Each slice represents the mean antibacterial drug consumption (in days of therapy per one thousand patient-days) of the corresponding antibacterial class as a percentage of the mean total antibacterial drug consumption.

Table 3.2 Summary of Antibacterial Drug Consumption Classified by Antibacterial Drug Class at 70 US Academic Medical Centers in 2009

	DOTs/1000 PDs		DOTs/1000 discharges	
Group	**Mean (SD)**	**Min-Max**	**Mean (SD)**	**Min-Max**
Vancomycin	128.4 (30.2)	42.6-194.2	705.7 (202.7)	191.3-1197.8
Fluoroquinolones	119.6 (38.9)	38.3-233	649.3 (212.0)	195.2-1087.5
β-lactam/β-lactamase inhibitor combinations	105.4 (37.9)	13.0-182.2	579.5 (231.4)	68.3-1159.4
1st generation cephalosporins	93.1 (33.5)	34.1-270.8	500.4 (149.8)	213.8-976.1
3rd and 4th generation cephalosporins	86.6 (34.9)	21.3-253.2	475.4 (206.5)	114.7-1440.9
Metronidazole	57.4 (19.6)	25.1-118	312.9 (110.0)	88.0-621.5
Carbapenems	39.1 (21.4)	8.5-100.5	218.0 (129.8)	31.9-606.7
Trimethoprim/sulfamethoxazole	35.1 (18.5)	5.0-91.2	194.8 (112.0)	28.5-626.2
Macrolides	31.7 (10.8)	11.6-59.4	171.6 (57.1)	58.0-314.3
Clindamycin	25.1 (10.0)	4.2-49.5	135.5 (54.9)	26.3-289.4
Other anti-Gram-positive agents	23.8 (12.5)	1.8-72.9	133.2 (79.2)	6.3-440.2
Aminoglycosides	23.5 (9.7)	9.8-58.6	127.8 (54.0)	46.2-320.8
β-lactamase sensitive penicillins	22.8 (9.8)	6.8-69.6	121.7 (43.2)	38.9-275.4
Tetracyclines	11.2 (6.4)	4.0-39.0	61.9 (37.9)	19.3-222.0
2nd generation cephalosporins	10.0 (9.3)	0-59.0	55.0 (51.5)	0-330.3
Antistaphylococcal penicillins	5.8 (3.9)	0.8-25.7	32.1 (22.6)	4.7-151.5
Miscellaneous	2.4 (2.7)	0-10.1	12.8 (14.7)	0-56.4
Total antibacterial consumption	821.2 (108.1)	560.8-1104.1	4487.6 (859.2)	2521.7-7579.5

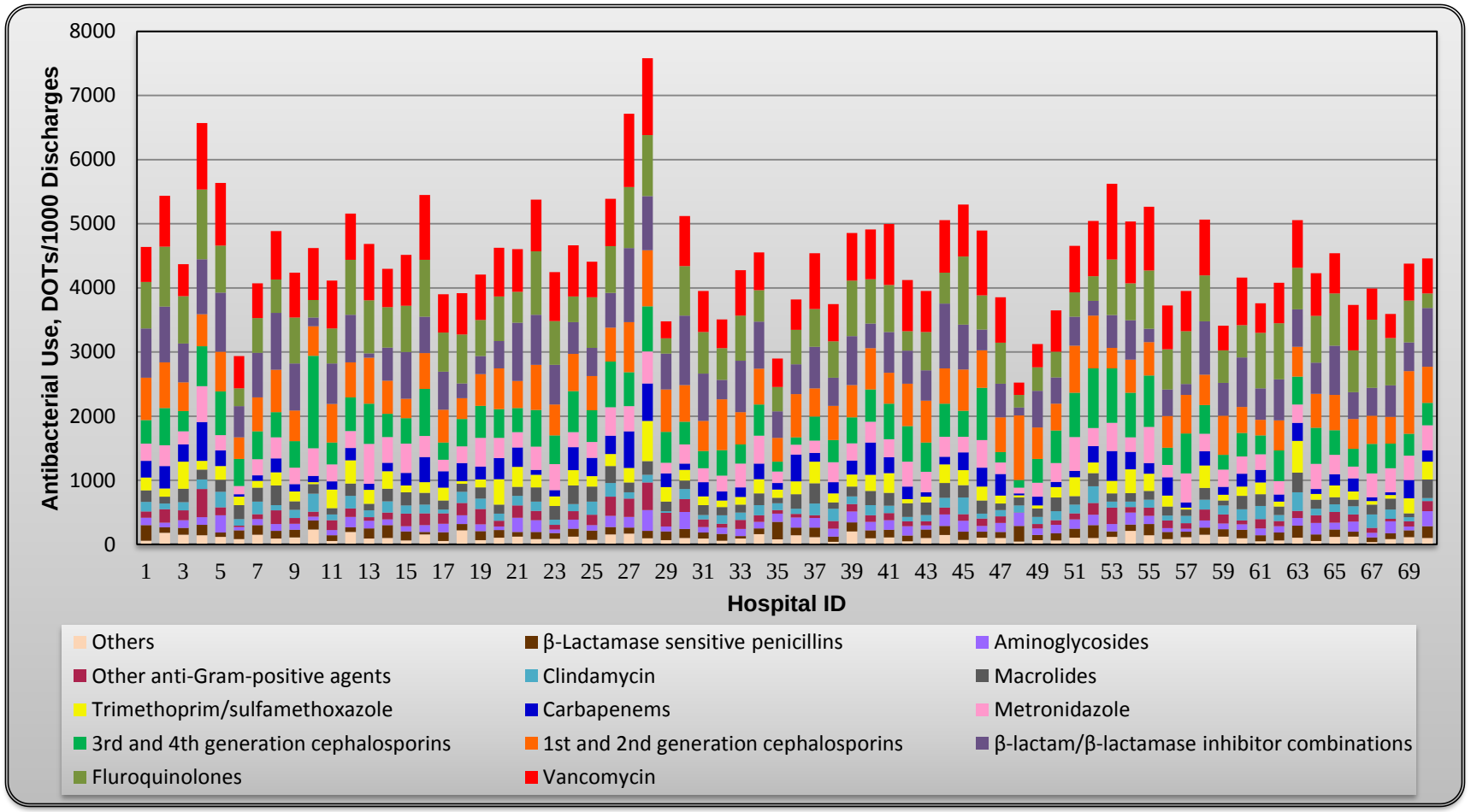
DOTs/1000 PDs, days of therapy per one thousand patient-days; DOTs/1000 discharges, days of therapy per one thousand discharges; SD, standard deviation

Figure 3.2 and Figure 3.3 depict the total AbC at each of the 70 hospitals broken down by antibacterial drug class and expressed as DOTs/1000 PDs and DOTs/1000 discharges, respectively. When the former rate was used, Hospital #29 had the lowest AbC with 560.8 DOTs/1000 PDs while hospital #48 had the lowest consumption when the latter rate was used with 2521.7 DOTs/1000 discharges. Hospital #28 had the highest total AbC with a rate of 1104.1 DOTs/1000 PDs (7597.5 DOTs/1000 discharges). The two figures indicate that a hospital's rank and whether it is perceived as an outlier may depend on the rate used to measure AbC. However, it is important to note that these are crude rates and that risk-adjusted AbC rates may provide a better reflection of hospital ranks and their outlier status.



Others: tetracyclines, antistaphylococcal penicillins, nitrofurantoin and sulfadiazine; Other anti-Gram-positive agents: linezolid, daptomycin and tigecycline

Figure 3.2 Crude antibacterial drug consumption rates (in days of therapy [DOTs] per one thousand patient-days [1000 PDs]) at 70 US academic medical centers in 2009. Each entire bar represents the total systemic antibacterial consumption at an individual hospital divided into 14 antibacterial classes.



Others: tetracyclines, antistaphylococcal penicillins, nitrofurantoin and sulfadiazine; Other anti-Gram-positive agents: linezolid, daptomycin and tigecycline

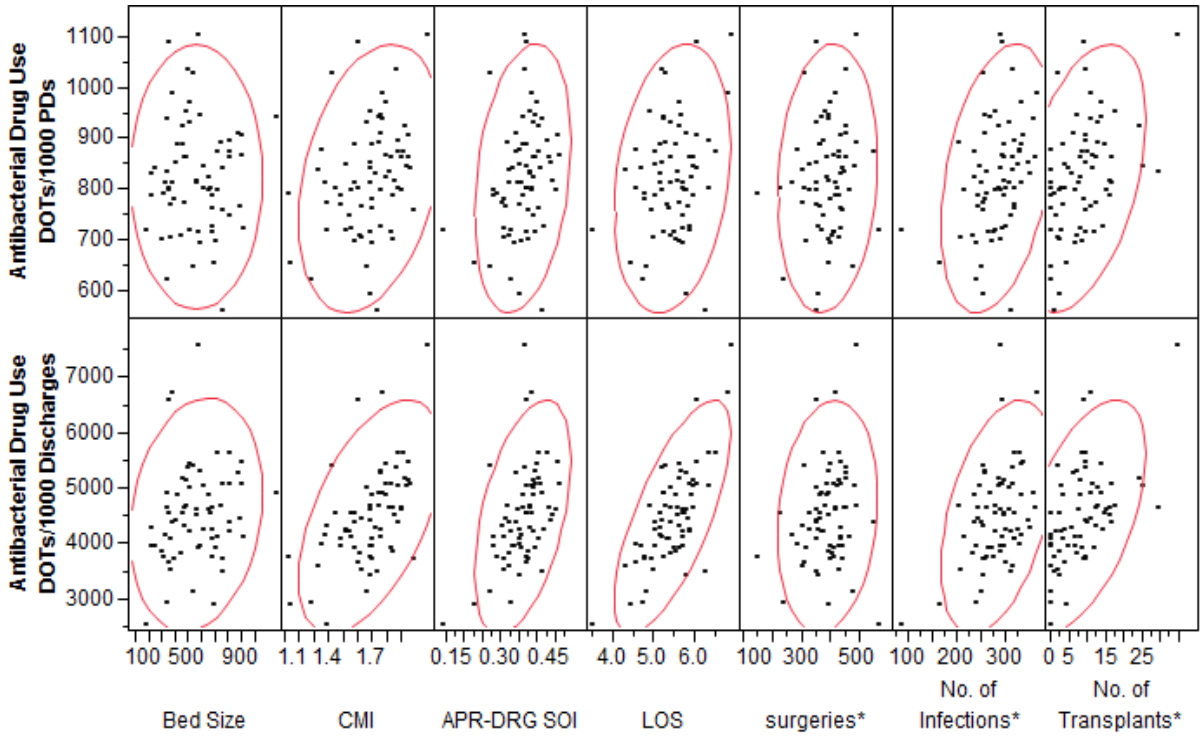
Figure 3.3 Crude antibacterial drug consumption rates (in days of therapy [DOTs] per one thousand discharges) at 70 US academic medical centers in 2009. Each entire bar represents the total systemic antibacterial consumption at an individual hospital divided into 14 antibacterial classes.

3.2.2 Variable Screening

Figure 3.4 represents the bivariate relationships between AbC –measured in both DOTs/1000 PDs and DOTs/1000 discharges- and 7 potential predictor variables. The Pearson correlation coefficients (r) and the respective p-values for the association between the two measures of the outcome variable –in the above order- and the potential predictor variables were as follows: bed size (r= -0.003, p-value= 0.98) and (r= 0.18, p-value= 0.14), CMI (r= 0.32, p-value= 0.007) and (r= 0.54, p-value< 0.001), percent of discharges assigned to the major and extreme levels of APR-DRG SOI classification (r=0.27, p-value= 0.02) and (r= 0.48, p-value< 0.001), number of surgeries per 1000 discharges (r= 0.13, p-value= 0.28) and (r= 0.16, p-value= 0.19), number of infections per 1000 discharges (r= 0.36, p-value= 0.002) and (r= 0.44, p-value< 0.001), number of transplants per 1000 discharges (r= 0.44, p-value< 0.001) and (r= 0.54, p-value< 0.001), and LOS (r= 0.24, p-value= 0.04) and (r= 0.72, p-value< 0.001). The potential collinearity between predictor variables is discussed in subsection 3.2.4.

The One-way ANOVA did not suggest that there were any significant differences in AbC between different geographic locations using either the DOTs/1000 PDs measure, $F(5,64)$= 1.0, p-value= 0.42 or the DOTs/1000 discharges measure, $F(5,64)$= 0.78, p-value= 0.57. Predictor variables that were significantly associated with either measure at α= 0.30 were considered for the model selection procedure. It was determined, through trial and

error, that there was no significant advantage for using the APR-DRG based measure over the CMI; therefore, the latter SOI measure was selected for the model selection stage. The infection rate, transplant rate, surgery rate and LOS were the other variables considered for the selection of Model I while, in addition to the CMI, all other 5 continuous variables were considered for the selection of Model II.



* Number of events per one thousand discharges, CMI= case-mix index, APR-DRG SOI= percent of discharges in major and extreme severity of illness levels according to All Patient Refined Diagnosis Related Group classification, LOS= length of stay

Figure 3.4 A scatterplot matrix showing bivariate relationships between two measures of total antibacterial consumption (days of therapy per one thousand patient-days [DOTs/1000 PDs] and days of therapy per one thousand discharges [DOTs/1000 discharges]) and 7 potential predictor variables**.** The red ellipses represent the 95% confidence limits. A narrow ellipsoid with a diagonal orientation reflects a strong correlation while a more circular vertically oriented ellipsoid reflects a weak correlation.

3.2.3 Model Selection

Before presenting the results of the model selection procedure, an overview of the selection criteria: R^2, adjusted R^2, MSE, PRESS statistic, Mallows' C_p, and AICc is warranted. The *coefficient of determination*, R^2, can be interpreted as the proportion of variation in the outcome variable explained by the regression model. It is the ratio of the regression sum of squares (SSR) to the total sum of squares (SST).

$$R^2 = \frac{\text{SSR}}{\text{SST}} = \frac{\sum_{i=1}^{n}(\hat{y}_i - \bar{Y})^2}{\sum_{i=1}^{n}(y_i - \bar{Y})^2} \tag{3.1}$$

where y_i is the measured outcome variable of the i^{th} data point (observation), $\hat{y}_i$ is the fitted value of the i^{th} data point, and $\bar{Y}$ is the mean y_i (i= 1, 2,..., n). Since

$$\text{SST} = \text{SSR} + \text{SSE} \tag{3.2}$$

where SSE is the error sum of squares, Equation 3.1 can alternatively be written as

$$R^2 = 1 - \frac{\text{SSE}}{\text{SST}} = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{Y})^2} \tag{3.3}$$

SST is fixed for a given sample of y_i and is independent of the fitted model. SSR goes up with each predictor added to the model while SSE goes down. Therefore, R^2 is not a useful criterion for the comparison of models that have different number of predictor variables since it always increases with the addition of new variables to the model.

The adjusted R^2 (R^2_{ADJ}) is a modification of the R^2 that adjusts for the number of variables in the model. Unlike R^2, the adjusted R^2 may drop when a variable is added to the model and increases only if the increment in R^2 outweighs the added penalty of introducing the additional variable. The adjusted R^2 is given by

$$R^2_{ADJ} = 1 - \frac{\text{SSE} / df_{ERROR}}{\text{SST} / df_{TOTAL}} = 1 - \frac{\text{SSE} / n\text{-}p}{\text{SST} / n\text{-}1} \tag{3.4}$$

where df_{ERROR} is the error degrees of freedom, df_{TOTAL} is the total degrees of freedom, and p is the number of parameters in the model including the intercept ($p = k + 1$).

MSE, denoted by $\hat{\sigma}^2$, is an unbiased estimator of the population variance (σ^2), provided that the fitted model is correct.

$$\hat{\sigma}^2 = \frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{n - p} \tag{3.5}$$

Equation 3.5 is just the numerator of the fraction term in Equation 3.4. It is easy to see that the model with the largest adjusted R^2 will also have the smallest MSE and that the ranks of candidate models by both criteria will be identical.

The i^{th} "raw" residual (e_i) is the difference between the i^{th} value of the outcome variable and the i^{th} fitted value obtained from the estimated regression equation.

$$e_i = y_i - \hat{y}_i \tag{3.6}$$

The i^{th} PRESS residual, on the other hand, is the difference between the i^{th} value of the outcome variable and the i^{th} predicted value obtained from a model fitted after setting aside the i^{th} data point. For notation, a "$_{-i}$" subscript is used to indicate that the analysis is carried out after setting aside the i^{th} data point. Using this notation, the i^{th} PRESS residual, $e_{i,-i}$, is given by

$$e_{i,-i} = y_i - \hat{y}_{i,-i} \tag{3.7}$$

where $\hat{y}_{i,-i}$ is the i^{th} adjusted (PRESS) predicted value; that is, the predicted value obtained from a model fitted without the i^{th} data point. This procedure of setting aside one data point at a time, fitting the model with the remaining $n-1$ data points, using the fitted model to calculate the predicted value for the data point that was set aside, reintroducing that data point to

the model, setting aside the next data point, and so on; this procedure is carried out sequentially for all n data points until all n PRESS residuals are obtained. Then, the PRESS statistic is the sum of squares of the PRESS residuals defined as

$$\text{PRESS} = \sum_{i=1}^{n} (e_{i,-i})^2 = \sum_{i=1}^{n} (y_i - \hat{y}_{i,-i})^2 \tag{3.8}$$

The calculation of PRESS may seem like a tedious and repetitive task. However, one does not need to run repeated regressions to calculate PRESS as the PRESS residuals can be easily obtained by fitting the pertinent model once using all n data points as explained in subsection 3.2.5. Unlike raw residuals, PRESS residuals are true prediction errors since $\hat{y}_{i,-i}$ are independent of y_i. The smaller the PRESS statistic, the better the predictive capabilities of the model.

The C_p statistic, proposed by Mallows [91], is given by

$$C_p = p + \frac{(n-p)(\hat{\sigma}^2 - \hat{\sigma}^2_{\text{FULL}})}{\hat{\sigma}^2_{\text{FULL}}} \tag{3.9}$$

where $\hat{\sigma}^2$ is the MSE of the model under consideration and $\hat{\sigma}^2_{\text{FULL}}$ is the MSE of the full model containing all k predictor variables. The fraction in the above equation is a measure of bias so large deviations of C_p above or under p indicate an underfit or overfit model, respectively. The smallest C_p that is

approximately equal to p is favorable. Obviously, for the full model, $\hat{\sigma}^2 = \hat{\sigma}^2_{\text{FULL}}$ and consequently $C_p = p$ so this should not be taken as evidence of the superiority of the full model.

AICc was introduced in 1989 by Hurvich and Tsai [92] as a correction for the small sample bias of the original Akaike Information Criteria (AIC) [93].

$$AICc = AIC + \frac{2(p+1)(p+2)}{n-p-2} \tag{3.10}$$

where

$$AIC = n\log\left(\frac{\text{SSE}}{n}+1\right) + 2(p+1) \tag{3.11}$$

AICc is a measure of model performance where a smaller value denotes a better fitting model. AICc and AIC converge as n increases but AICc is preferred for small samples, particularly when n/p <40 for the full model. AICc seeks the most parsimonious model; the one that explains most of the variability with the least complexity. It does so by addressing the trade-off between bias (underfitting) and variance (overfitting). AICc is not an absolute measure but it is useful for the purpose of comparing different models providing they are based on the same dataset. If the AICc values of two models differ by more than 2, the model with the lower AICc is considered to have the better fit.

The all possible regressions procedure fitted 31 (i.e., 2^5-1) candidate models for the selection of Model I and 63 (i.e., 2^6-1) candidate models for the selection of Model II (the intercept- only models were not considered). The 5 "best" candidate models for both Model I and Model II according to the six selection criteria are presented in Table 3.3. For Model I, the table reveals that the candidate model that includes the transplant rate and the infection rate as predictor variables (Model IA) is superior to all other competing models. Moreover, this model was selected by the forward selection, the backward elimination and the stepwise regression procedures. Accordingly, Model IA was selected to represent Model I since its parsimony does not greatly sacrifice its performance.

Similarly, the selection of a candidate model to represent Model II was an obvious one since the selection criteria of the candidate model that includes the transplant rate, infection rate and LOS (Model IIA) were superior to those of the other four competing models. It was also the model selected by all three sequential selection procedures. Thus, Model IIA was selected to represent Model II. It should be noted that the candidate models of Model II that have bed size as one of the potential predictor variables are based on 67 observations only. Therefore, their selection criteria are not generally comparable with those of the models that do not include bed size which are based on the entire sample of 70 observations.

The parameter estimates and the VIFs for Model I and Model II are listed in Table 3.4. The predicted AbC rate for Model I was found to be 541.57 + 6.54 * number of transplants/1000 discharges + 0.79 * number of infections/1000 discharges. This model accounted for 31% of the variability in AbC measured in DOTs/1000 PDs ($F(2,67)= 15.3$, p-value< 0.001). The predicted AbC rate for Model II was found to be – 1116.61 + 40.71 * number of transplants/1000 discharges + 4.34 * number of infections/1000 discharges + 739.88 * LOS. This model accounted for 64% of the variability in AbC measured in DOTs/1000 discharges ($F(3,66)= 39.4$, p-value< 0.001).

Table 3.3 Selection Criteria of Candidate Models that Predict Total Hospital Antibacterial Drug Consumption Measured in Days of Therapy Per One Thousand Patient-days (Model I) and Days of Therapy Per One Thousand Discharges (Model II)

		Potential Predictor Variables						Selection Criteria				
Model ID	***P***	**Bed size**	**CMI**	**LOS**	**Surgery rate***	**Infection rate***	**Transplant rate***	**R^2 (adjusted R^2)**	**MSE**	**PRESS**	***C_p***	**AICc**
I A	3					X	X	0.31 (0.29)	8252	607953	1.9	835.48
I B	4				X	X	X	0.32 (0.29)	8290	616367	3.2	837.07
I C	4			X		X	X	0.32 (0.29)	8307	622733	3.3	837.21
I D	4		X			X	X	0.31 (0.28)	8372	621238	3.8	837.76
I E	5		X		X	X	X	0.33 (0.29)	8280	620222	4.1	838.31
II A	4			X		X	X	0.64 (0.63)	276490	21237012	3.2	1035.54
II B	5			X	X	X	X	0.65 (0.63)	276600	21347446	4.3	1036.90
II C	5	X		X		X	X	0.65 (0.63)	273484	20606183	4.5	1037.11
II D	5		X	X		X	X	0.64 (0.62)	280739	21789440	5.2	1037.92
II E	6	X		X	X	X	X	0.66 (0.63)	272829	20677235	5.3	1038.36

* number of events per one thousand discharges, p= number of parameters in the model including intercept; CMI= case-mix index, LOS= length of stay, MSE= mean square error, PRESS= PRESS statistic, C_p= Mallows' C_p statistic, AICc= corrected Akaike information criterion

Table 3.4 Parameter Estimates and Variance Inflation Factors of Model I and Model II

	Model I [y= days of therapy per 1000 patient-days]						
Term	**Estimate**	**SE**	***t***	**p-value**	**95% CI**		**VIF**
Intercept	541.57				406.09	677.05	
No. of transplants*	6.54	1.53	4.27	<.001	3.48	9.60	1.00
No. of infections*	0.79	0.23	3.38	.0012	0.32	1.26	1.00
	Model II [y= days of therapy per 1000 discharges]						
Intercept	-1116.61				-2409.88	176.67	
No. of transplants*	40.71	9.79	4.16	<.001	21.17	60.25	1.22
No. of infections*	4.34	1.49	2.92	.0048	1.37	7.30	1.20
LOS	739.88	132.15	5.60	<.001	476.036	1003.72	1.43

*Per one thousand discharges, SE= standard error, CI= confidence interval, VIF= variance inflation factor, LOS= length of stay

3.2.4 Checking for Multicollinearity

Multicollinearity refers to the correlation between predictor variables and exists to a troublesome degree when two or more predictor variables have a very strong linear association. Multicollinearity results in unstable parameter estimates in terms of magnitude and sign. Another impact of multicollinearity is that it lowers the power of the partial t-tests of the parameter estimates involved in the multicollinearity as a consequence of inflating the standard errors of these parameter estimates.

The pairwise correlations between the predictor variables are presented in Table 3.5. The highest correlation is the one between the CMI and surgery rate (r= 0.62). While this correlation is relatively high, a correlation with an absolute value ≥ 0.90 is usually required for multicollinearity to be a serious problem. However, a high pairwise correlation is a sufficient but not a necessary condition for multicollinearity. That is, a very high pairwise correlation indicates a serious multicollinearity problem but its absence does not rule out the possibility of a multicollinearity problem. A more accurate assessment of multicollinearity can be attained by examining the VIFs (Table 3.4). VIFs measure the inflation of the variances of the parameter estimates above and beyond the ideal situation where multicollinearity is completely non-existent (VIF= 1).

The VIF of the j^{th} predictor variable is given by

$$\mathrm{VIF}_j = \frac{1}{1 - R_j^2} \tag{3.12}$$

where R_j^2 is the R^2 obtained from regressing the j^{th} predictor variable on all the other predictor variables. As a rule of thumb, a VIF ≥4 indicates a potential multicollinearity problem while a VIF ≥10 indicates the presence of a severe multicollinearity problem. Since all VIFs are well below 4, multicollinearity is unlikely to be present to a detrimental degree in either Model I or Model II.

Table 3.5 Pairwise Correlations between Predictor Variables

Variable	1	2	3	4	5	6
1. Bed size	1					
2. CMI	0.36	1				
3. LOS	0.42	0.58	1			
4. No. of surgeries*	0.18	0.62	0.09	1		
5. No. of infections*	-0.07	0.24	0.38	-0.27	1	
6. No. of transplants*	0.18	0.59	0.4	0.35	0.03	1

* Per one thousand discharges, CMI= case-mix index, LOS= length of stay

3.2.5 Analysis of Residuals

The analysis of residuals is carried out to identify observations that exert undue influence on the regression. Residuals are also useful in checking the assumptions underlying linear regression. This subsection is devoted to identifying outliers and influential observations while their influence on Model I and Model II is discussed in the next section.

In order to discuss analysis of residuals and influence diagnostics, it is helpful to introduce the general linear regression model in matrix notation,

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon} \tag{3.13}$$

$$\mathbf{y} = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}, \quad \mathbf{X} = \begin{bmatrix} 1 & x_{11} & x_{12} & \cdots & x_{1k} \\ 1 & x_{21} & x_{22} & \cdots & x_{2k} \\ \vdots & \vdots & \vdots & \cdots & \vdots \\ 1 & x_{n1} & x_{n2} & \cdots & x_{nk} \end{bmatrix}, \quad \boldsymbol{\beta} = \begin{bmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_k \end{bmatrix}, \quad \boldsymbol{\varepsilon} = \begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \vdots \\ \varepsilon_n \end{bmatrix}$$

Where $\mathbf{y}$ is an $n\times1$ vector of values of the outcome variable, $\mathbf{X}$ is an $n\times p$ full column rank matrix of known predictor variables that may include a constant, $\boldsymbol{\beta}$ is a $p\times1$ vector of unknown parameters to be estimated, and $\boldsymbol{\varepsilon}$ is an $n\times1$ vector of random errors that are independent and identically distributed (i.i.d) with mean zero and a constant but unknown variance σ^2.

The vector of fitted values, denoted by $\hat{\mathbf{y}}$, is given by

$$\hat{\mathbf{y}} = \mathbf{X}\hat{\boldsymbol{\beta}} \tag{3.14}$$

where $\hat{\boldsymbol{\beta}}$ is the vector of ordinary least squares (OLS) parameter estimates given by

$$\hat{\boldsymbol{\beta}} = \left(\mathbf{X}'\mathbf{X}\right)^{-1}\mathbf{X}'\mathbf{y} \tag{3.15}$$

where $\mathbf{X}'$ is the transpose of the matrix $\mathbf{X}$ and $\left(\mathbf{X}'\mathbf{X}\right)^{-1}$ is the inverse of $\left(\mathbf{X}'\mathbf{X}\right)$. Substituting Equation 3.15 into Equation 3.14

$$\hat{\mathbf{y}} = \mathbf{X}\left(\mathbf{X}'\mathbf{X}\right)^{-1}\mathbf{X}'\mathbf{y} \tag{3.16}$$

Equation 3.16 can be rewritten as

$$\hat{\mathbf{y}} = \mathbf{H}\mathbf{y} \tag{3.17}$$

where

$$\mathbf{H} = \mathbf{X}\left(\mathbf{X}'\mathbf{X}\right)^{-1}\mathbf{X}' \tag{3.18}$$

$\mathbf{H}$ is a symmetric ($\mathbf{H}'=\mathbf{H}$) and an idempotent ($\mathbf{H}^2=\mathbf{H}$) matrix known as the "Hat" matrix. The diagonal elements of $\mathbf{H}$, called the Hat diagonals (h_{ii}), play a central role in regression diagnostics. The h_{ii} value is a measure of *leverage* where the leverage of the i^{th} data point is the standardized distance from that point to the center of the data in the x's. A data point

with a large h_{ii} is a high leverage point or an extreme point in the x direction. It can be shown that for a model with an intercept term, $\frac{1}{n} \leq h_{ii} \leq 1$ and [94]

$$\sum_{i=1}^{n} h_{ii} = p \qquad (3.19)$$

where p is the number of model parameters. Then, the average size of h_{ii} equals p/n and a data point with a $h_{ii} \geq 2p/n$ (twice the average size) may be considered as a high leverage point [95]. Applying this cut-off to Model I (p= 3, n= 70), potential high leverage points were identified as those hospitals that had $h_{ii} \geq 0.0857$ while for Model II (p= 4, n= 70), hospitals that had $h_{ii} \geq 0.114$ were considered as potential high leverage points. Figure 3.5 plots h_{ii} against the predicted total AbC for Model I (Figure A) and Model II (Figure B). Both models identified Hospitals #20, #28, #35, and #48 as potential high leverage points while Hospital #54 was identified by the former model only. High leverage points do not necessarily exert undue influence on the regression model as will be explained shortly. Also, those high leverage points that do have a substantial influence on the model may be labeled as "good" if they improve the model fit and "bad" if they hurt it.

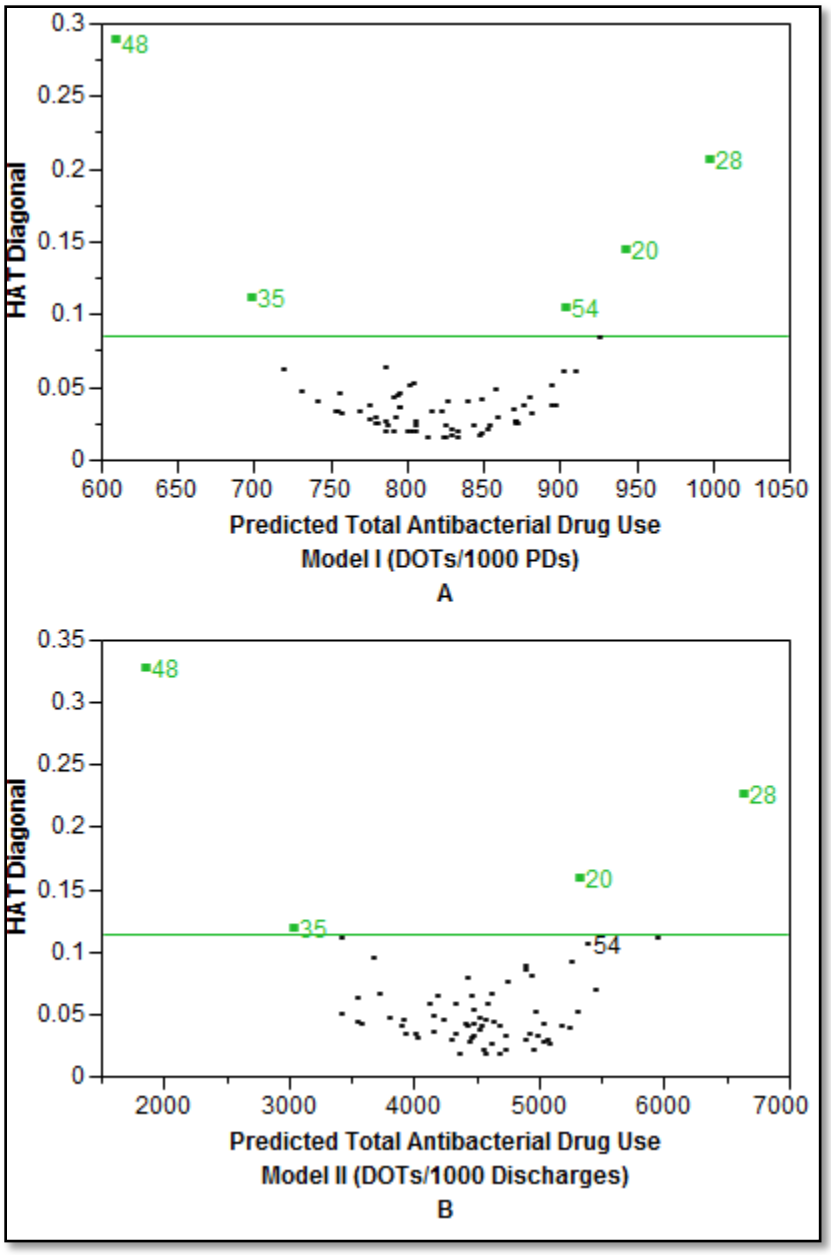


Figure 3.5 Plots of Hat diagonals versus predicted total antibacterial drug consumption showing potential high leverage points of Model I (Figure A) and Model II (Figure B). The green horizontal lines represent the cut-off points of the Hat diagonals (2p/n) above which data points are considered to be high leverage points (green data points). The two models identified the same hospitals as being potential high leverage points with the exception of Hospital #54 which was identified by Model I only.

As mentioned in subsection 3.2.3, there is no need to run multiple regressions to calculate the PRESS residuals. It turns out that the PRESS residual is a function of the raw residual and the Hat diagonal. The i^{th} PRESS residual can be calculated from fitting a single regression model with all n data points using the following equation

$$e_{i,-i} = \frac{e_i}{1-h_{ii}} \tag{3.20}$$

Whereas a high leverage point is extreme in the x direction, an *outlier* is a data point that is extreme in the y direction given its x values. That is, an outlier is a data point with a large residual. By substituting Equation 3.17 into the matrix form of Equation 3.6, it is easy to show that the vector of residuals, **e**, can be written as

$$\mathbf{e = (I - H)y} \tag{3.21}$$

Where **I** is an $n \times n$ identity matrix. Accordingly, the variance of e_i is given by

$$var(e_i) = \sigma^2(1-h_{ii}) \tag{3.22}$$

The residuals (e_i) are estimates of the errors (ε_i) and should ideally behave like them. However, the constant variance assumption that is made on ε_i does not generally hold for e_i as can be seen from Equation 3.22. The variance of e_i is smaller for a data point that is remote from the data center (large h_{ii}) than that of a data point near the data center (small h_{ii}).

Also, since e_i sum to zero, they are necessarily not independent. Therefore, raw residuals are not optimal for serving as diagnostic tools or detecting outliers.

Standardization of the raw residuals by dividing them by their standard errors creates a scale-free statistic with zero mean and unit standard deviation. The standard error of e_i is the square root of Equation 3.22. Hence, the i^{th} standardized residual, also known as a *studentized residual* (r_i), is

$$r_i = \frac{y_i - \hat{y}_i}{\hat{\sigma}\sqrt{1 - h_{ii}}} \tag{3.23}$$

where $\hat{\sigma} = \sqrt{\text{MSE}}$. Studentized residuals are leverage (location) independent, and accordingly can be validly compared among each other. It is worth mentioning that standardization of the PRESS residual given in Equation 3.7 yields the studentized raw residual in Equation 3.23 [96]. They are called studentized residuals because they follow a *t*-like distribution. They do not follow an exact *t*-distribution because of the dependence between the numerator and denominator of Equation 3.23. This dependence can be eliminated by replacing $\hat{\sigma}$ with $\hat{\sigma}_{-i}$ which is just $\sqrt{\text{MSE}}$ of the model fitted without the i^{th} data point. This creates the *externally studentized residual*, often called *R*-student (t_i), which is given by

$$t_i = \frac{y_i - \hat{y}_i}{\hat{\sigma}_{-i}\sqrt{1-h_{ii}}} \tag{3.24}$$

As with the PRESS residual, there is no need to fit multiple regression models to calculate $\hat{\sigma}_{-i}$. $\hat{\sigma}_{-i}$ can be calculated by fitting a single regression model with all n data points as follows

$$\hat{\sigma}_{-i} = \sqrt{\frac{(n-p)\hat{\sigma}^2 - e_i^2/(1-h_{ii})}{n-p-1}} \tag{3.25}$$

If the standard assumptions, including normality, on the ε_i are satisfied, then *R*-student follows t_{n-p-1} which is an exact *t*-distribution with *n*-*p*-1 degrees of freedom (*df*). Therefore, it makes more sense to use the critical points from student's *t*-distribution for t_i than it does for r_i. The i^{th} data point is considered a potential outlier if $|t_i| > t_{\alpha/2,n-p-1}$.

For both Model I (*df*= 66) and Model II (*df*= 65), the critical value at α= .05 was ±1.997 while the corresponding value at α= .10 was ±1.669. Hospitals whose t_i were as or more extreme than these critical values were identified as potential outliers at the respective significance level as shown in Figure 3.6. At α=.05, both models identified Hospitals #4 and #26 as potential high outliers while Hospital #28 was identified by Model II only. Hospital #22 was identified as a potential high outlier by Model I at the same significance level whereas it was identified by Model II at α=.10. Also

at α=.10, both models identified Hospital #45 as a potential high outlier. Both models identified Hospital #29 at α=.05 and Hospital #59 at α=.10 as potential low outliers. In addition to their value in identifying outliers, residual by predicted plots such as Figure 3.6 are also useful in the detection of violations of some of the assumptions of linear regression as explained in the next subsection.

It can be argued that a Bonferroni-type correction may be warranted when using R- student to detect outliers since this approach involves simultaneous testing of multiple data points. Therefore, one should arguably compare all n values of t_i with the more conservative critical value of the t-distribution $t_{(\alpha/2n),n-p-1}$ rather than the uncorrected critical value $t_{\alpha/2,n-p-1}$. However, it is probably best to view R-student as a diagnostic rather than a hypothesis–testing tool. That is, only relatively crude-off points need to be considered and suspect data points should be closely examined regardless of statistical significance.

Another commonly used method for detecting potential outliers involves the construction of prediction intervals around the predicted values at the desired confidence level. One then determines the observations whose observed values fall above the upper limit or below the lower limit of the corresponding prediction interval and identifies them as high or low outliers, respectively. Figure 3.7 depicts the observed AbC rates along with the 95%

and 90% prediction intervals of Model I and Model II. As illustrated in the figure, the identity of hospitals that were identified as outliers and the confidence level at which they were declared as outliers differed from the R-student method in Figure 3.6. When a suspected outlier is included in the calculation of its corresponding prediction interval, one runs the risk of missing some outliers. This is because a point with a large residual would inflate the MSE and consequently results in wider prediction intervals. Therefore, as indicated earlier, one should leave out the observation in question when trying to determine if it is an outlier. Since R-student is the more sensitive method, it was the one adopted for the detection of outliers in this project.

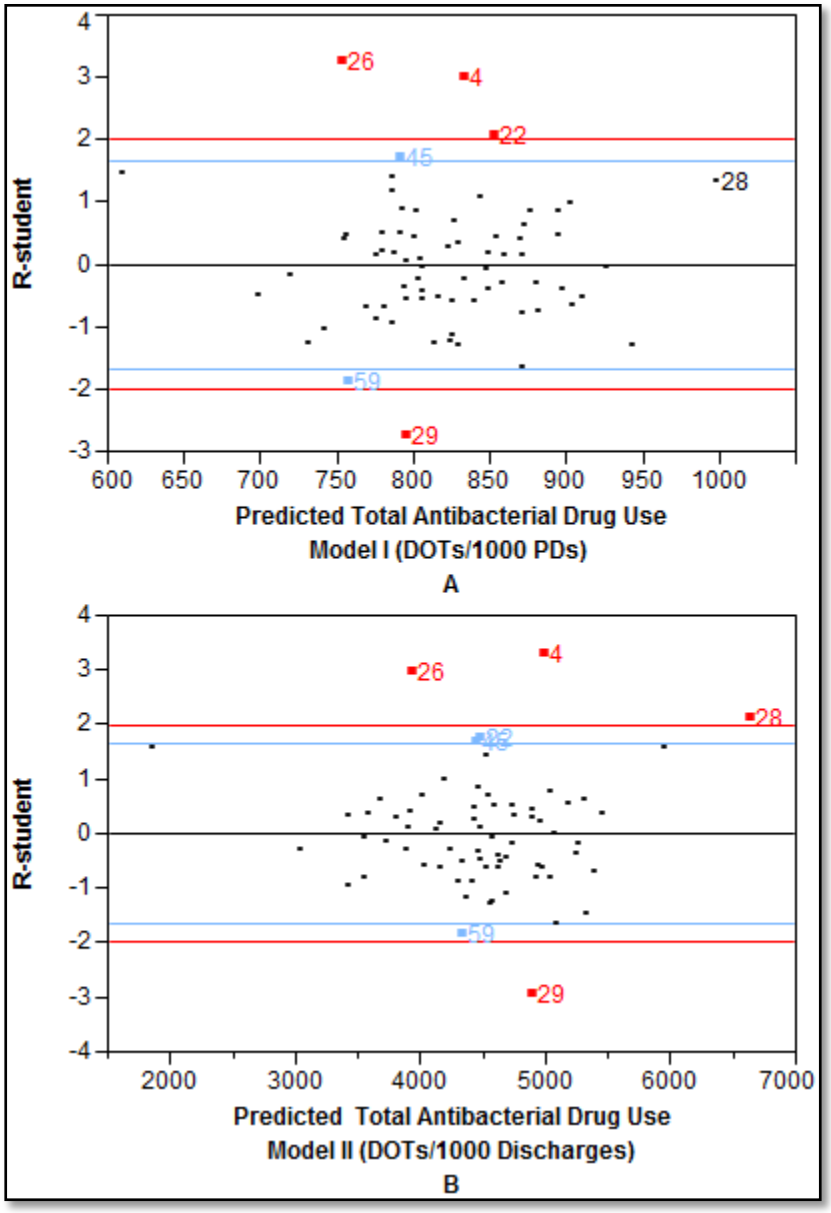


Figure 3.6 Plots of externally studentized residuals (R-student) versus predicted total antibacterial drug consumption showing potential outlier hospitals identified by Model I (Figure A) and Model II (Figure B). The red reference lines and the blue reference lines represent the critical values of the t-distribution with n-p-1 degrees of freedom at the 95% and 90% confidence levels, respectively. The red data points represent potential outliers at α=.05 while the blue data points represent potential outliers at α=.10. The two models identified the same hospitals with the exception of Hospital #28 which was identified as a potential high outlier by Model II only and Hospital #22 which was identified as a potential high outlier by Model I at α=.05 while it was identified by Model II at α=.10. These plots are also useful for detecting violations in some of the assumptions of linear regression as explained in the next section. These plots should ideally reveal a random scattering of the studentized residuals around 0 (black line).

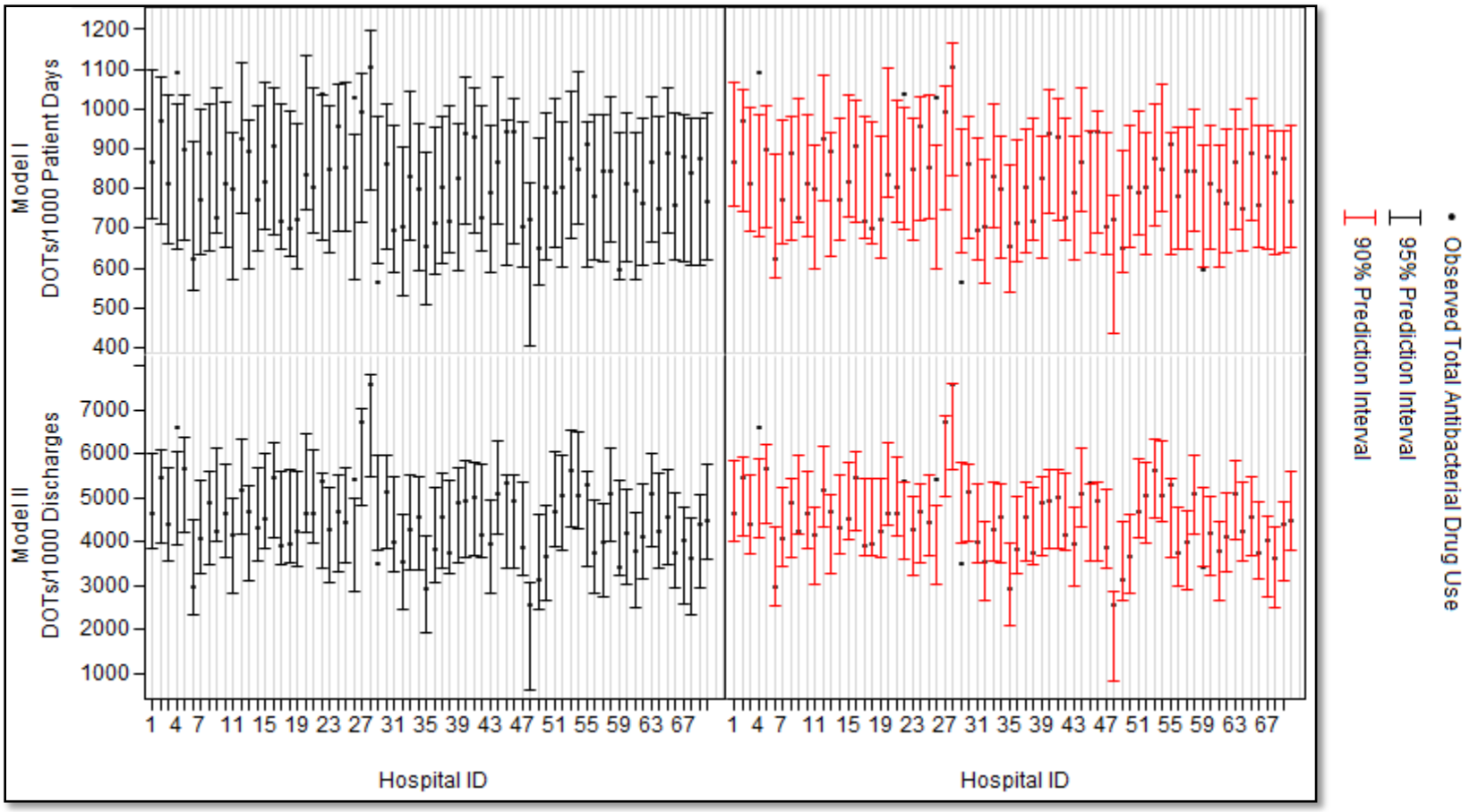


Figure 3.7 Observed antibacterial drug consumption along with the 95% and 90% prediction intervals of Model I (upper panel) and Model II (lower panel). At the 95% confidence level, Hospitals #4 and #26 were identified as potential high outliers while Hospital #29 was identified as a potential low outlier by both models. At the 90% confidence level, Hospital #22 was identified as a potential high outlier while Hospital #59 was identified as a potential low outlier by both models.

A data point is considered to be influential if its exclusion from a model results in a noticeable change in the performance of that model or its various regression statistics. Figure 3.8 (B) demonstrates that an outlier is not necessarily influential (depends on leverage). A high leverage point may or may not be influential as illustrated in Figure 3.8 (A) and Figure 3.8 (B), respectively. In fact, the most influential data points are those that have both high leverage and large residuals as illustrated in Figure 3.8 (B). This implies that Hospital #28 is a high influence point in Model II and, perhaps to a lesser extent, in Mode I. Other data points that are considered high influence points include, but are not limited to, Hospitals #20 and #48 in both models as they have both large residuals and high leverage despite not being labeled as either outliers or high leverage points. The influential status of such data points can be verified by the inspection of the various influence diagnostics which are discussed next.

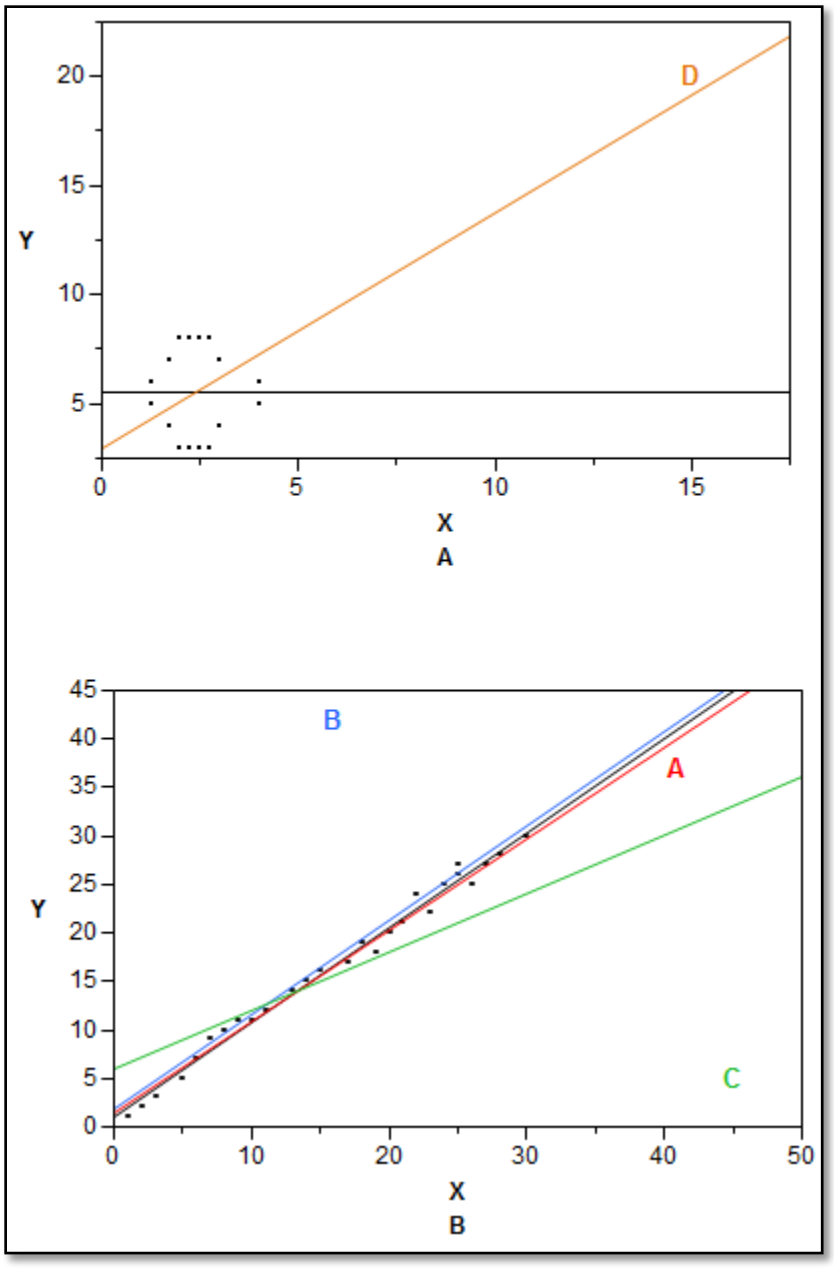


Figure 3.8 Different scenarios of outliers, high leverage points, and their influence on the fit of the model. Figure A, the black line was fitted using the black data points while the orange line was fitted using the same data points in addition to point D which is a high leverage point. Clearly, point D is a high influence point that has a positive impact on the fit of the model. Figure B, the black line was fitted using the black data points only. The red line was fitted using the same data points in addition to point A which is a high leverage point but not an outlier. The influence of point A on the regression is minimal since it falls along the general trend of the rest of the data. The blue line was fitted with the black data points in addition to point B which is an outlier but exhibits low leverage. The blue line is parallel and near the black one indicating that point B does not exert undue influence on the regression. The green line was fitted using the black data points in addition to point C which is both a high leverage point and an outlier. It is obvious that Point C is a high influence point that has a negative impact on the fit of the model.

3.2.6 Influence Diagnostics

Having identified potential high leverage points, outliers and high influence points, this subsection is devoted to determining the influence of such suspect data points, if present, on the regression model. This is accomplished by examining various influence diagnostics. Influence diagnostics measure the impact of each data point on model performance. More specifically, these diagnostics measure the extent by which each data point contributes to the magnitude of parameter estimates and the prediction of fitted values.

(i) *Influence on the Fitted Value (DFFITS)*

DFFITS, which stands for "**D**i**F**ference in **FIT**, **S**tandardized", was first proposed in 1980 by Belsley et al. [97]. It represents (roughly) the number of standard errors that the fitted value of the i^{th} data point ($\hat{y}_i$) changes after refitting the model without the i^{th} data point. Since the variance of $\hat{y}_i$ is given by

$$\text{Var}(\hat{y}_i) = \hat{\sigma}^2 h_{ii} \tag{3.26}$$

then the i^{th} DFFITS is given by

$$(\text{DFFITS})_i = \frac{\hat{y}_i - \hat{y}_{i,-i}}{\hat{\sigma}_{-i}\sqrt{h_{ii}}} \tag{3.27}$$

It turns out that DFFITS can be expressed as a function of R-student and h_{ii}

$$(\text{DFFITS})_i = (R\text{-student})_i \left[\frac{h_{ii}}{1-h_{ii}} \right]^{1/2} \tag{3.28}$$

A rule of thumb is to consider the i^{th} data point as having a high influence on the fitted value if $|(\text{DFFITS})_i| \geq 2\sqrt{p/n}$.[97] According to this rule, the cut-off value for Model I is ±0.414 while the corresponding value for Model II is ±0.478. Figure 3.9 represents plots of $(\text{DFFITS})_i$ versus predicted (fitted) values of the two models. As shown in the figure, Hospitals #20, #26, #28, #29 and #48 exceed the cut-offs of both models while Hospitals #4 and #27 exceed the cut-off of Model II only. As evident in the figure, Hospital #48 in both models and Hospital #28 in Model II have $(\text{DFFITS})_i$ values that are considerably more extreme than those of the rest of the hospitals.

One may be interested in expressing the influence of the i^{th} data point on its fitted value in terms of the units of the outcome variable. This can be accomplished by multiplying $(\text{DFFITS})_i$ by the standard error of prediction of the i^{th} data point which is the square root of Equation 3.26 with $\hat{\sigma}_{-i}$ used in place of $\hat{\sigma}^2$. Obviously, this expression of the prediction error is also the denominator of $(\text{DFFITS})_i$ in Equation 3.27 and multiplying DFFITS by its denominator yields $\hat{y}_i - \hat{y}_{i,-i}$ which is the difference in the fitted value of the i^{th} data point when the i^{th} data point is included in the model and when it is removed from it.

For Model I, $(DFFITS)_{48} = 0.93$ indicates that the removal of Hospital #48 from Model I decreases its predicted outcome by 0.93 standard errors. Transforming this difference into units of the outcome variable as explained above, one concludes that the presence of Hospital #48 in Model I decreases the predicted AbC of this hospital by 45 DOTs/1000 PDs. For Model II, $(DFFITS)_{48} = 1.10$ indicates that the removal of Hospital #48 from Model II decreases its predicted outcome by 1.10 standard errors which is equivalent to 328.4 DOTs/1000 discharges.

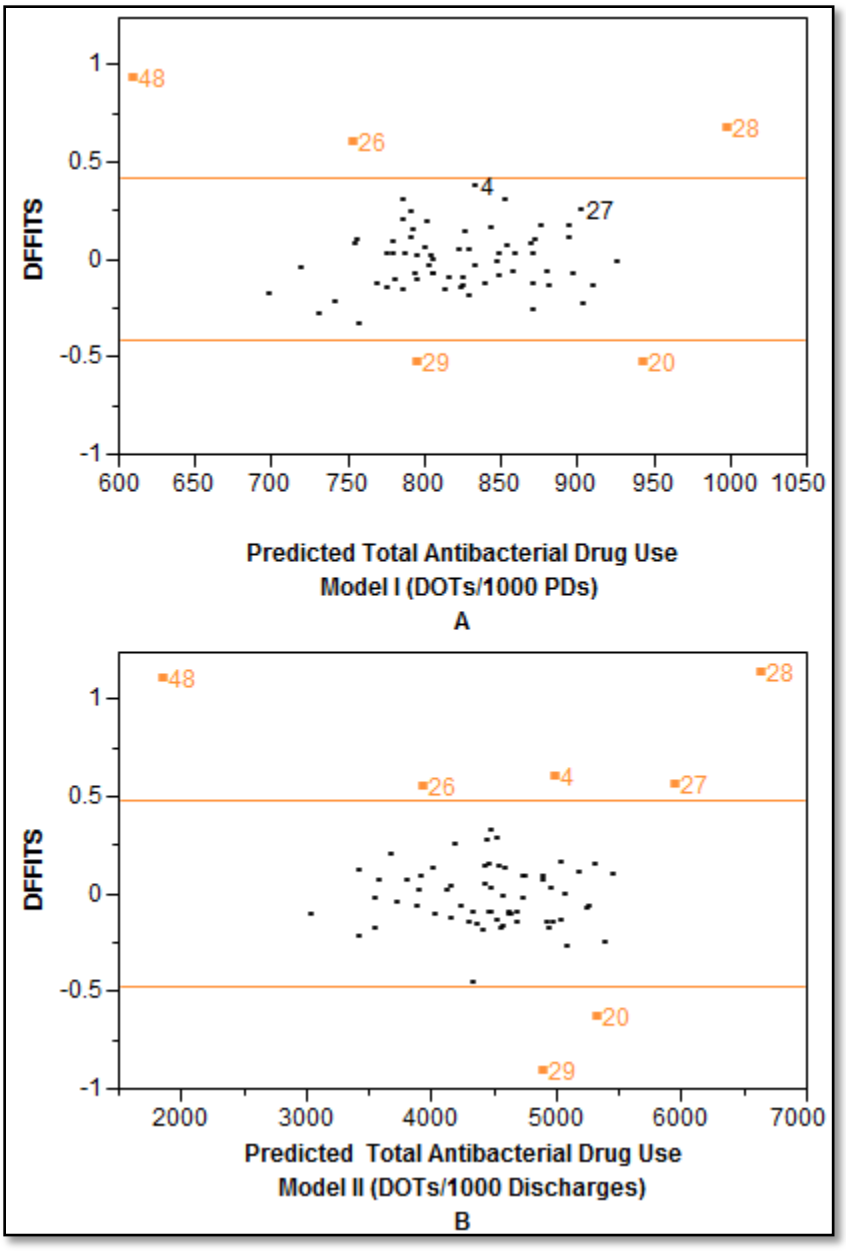


Figure 3.9 Plots of DFFITS versus predicted (fitted) total antibacterial drug consumption for Model I (Figure A) and Model II (Figure B). The orange lines represent the cut-off $\pm 2\sqrt{p/n}$ (± 0.414 for Model I and ± 0.478 for Model II). The orange data points exceed these cut-off values and are therefore considered to have high influence on their fitted values.

(ii) *Influence on the Parameter Estimates (DFBETAS)*

DFBETAS measures the number of standard errors that the j^{th} parameter estimate $(\hat{\beta}_j)$ changes after refitting the model without the i^{th} data point.

Since the variance of $\hat{\beta}_j$ is given by

$$\mathrm{Var}(\hat{\beta}_j) = \sigma^2 (X'X)^{-1} \tag{3.29}$$

Then the influence of the i^{th} data point on the j^{th} parameter estimate is given by

$$(\mathrm{DFBETAS})_{j,i} = \frac{\hat{\beta}_j - \hat{\beta}_{j,-i}}{\hat{\sigma}_{-i}\sqrt{c_{jj}}} \tag{3.30}$$

where $\hat{\beta}_{j,-i}$ is the j^{th} parameter estimate of the model fitted without the i^{th} data point and c_{jj} is the j^{th} diagonal element of $(X'X)^{-1}$. Like DFFITS, DFBETAS can be expressed as a function of R-student and h_{ii} allowing its computation from the original regression with all n data points without the need of fitting multiple models. However, the formula is more complex than that of DFFITS and the reader is referred to Myers for details [94]. A rule of thumb is to consider the i^{th} data point as having a high influence on the j^{th} parameter estimate if $|(\mathrm{DFBETAS})_{j,i}| \geq 2/\sqrt{n}$. [97] According to this rule, the cut-off value is ±0.239 for both Model I and Model II. The DFBETAS for Model I are listed in Table 3.6 while those for Model II are listed in Table 3.7.

The values in boldface in the two tables indicate $|(\text{DFBETAS})_{j,i}| \geq 0.239$ and are therefore likely to exert a high influence on the parameter estimates. Unsurprisingly, the data points with the most extreme DFBETAS are the ones that were identified as having the most extreme DFFITS (Hospital #48 in Model I and Hospitals #48 and #28 in Model II). In Model I, the removal of Hospital #48 increases the parameter estimate of infection rate by 0.87 standard errors. In Model 2, the removal of Hospital #48 increases the parameter estimate of the same variable by 0.74 standard errors while removing Hospital #28 decreases the parameter estimate of transplant rate by 0.81 standard errors. $(\text{DFBETAS})_{j,i}$ can be transformed (by making use of the standard error of the parameter estimates) to reflect the influence of the i^{th} data point on the j^{th} parameter estimates in terms of the unit of the outcome (DOTs/1000 PDs or DOTs/1000 discharges).

Table 3.6 DFBETAS for Model I

Hospital ID	DFBETAS Transplant Rate	DFBETAS Infection Rate	Hospital ID	DFBETAS Transplant Rate	DFBETAS Infection Rate
1	-0.031	-0.113	36	0.017	0.090
2	0.073	0.106	37	-0.010	0.007
3	-0.059	0.038	38	-0.024	0.021
4	0.008	0.094	39	-0.003	-0.061
5	0.004	0.040	40	0.015	0.090
6	0.181	0.137	41	0.047	0.043
7	0.050	-0.054	42	0.015	-0.032
8	-0.067	0.093	43	-0.020	0.005
9	-0.151	-0.070	44	-0.051	-0.030
10	0.005	-0.015	45	-0.042	-0.112
11	-0.013	-0.080	46	0.093	-0.041
12	-0.013	0	47	0.101	-0.020
13	0.098	**-0.255**	48	-0.221	**-0.872**
14	-0.040	0.044	49	0.150	0.081
15	-0.096	-0.025	50	0.003	-0.002
16	0.003	0.059	51	-0.078	0.062
17	-0.078	0.064	52	-0.016	0.002
18	-0.003	0.036	53	0	0.017
19	0.069	0.002	54	-0.201	0.071
20	**-0.500**	0.091	55	-0.056	-0.087
21	-0.088	-0.014	56	-0.002	0.016
22	0.025	0.172	57	-0.030	0.009
23	-0.024	0.031	58	-0.004	-0.001
24	0.132	-0.014	59	0.200	0.136
25	-0.004	-0.054	60	-0.012	0.011
26	**-0.370**	**-0.240**	61	-0.051	-0.021
27	0.034	0.214	62	0.056	-0.037
28	**0.649**	0.010	63	0.008	0.005
29	**0.359**	-0.214	64	0.071	-0.044
30	-0.004	0.014	65	0.016	0.005
31	0.026	0.099	66	-0.010	0.039
32	0.019	0.033	67	-0.129	0.107
33	0.017	-0.057	68	-0.077	0.046
34	-0.022	0.000	69	0.023	-0.109
35	0.035	0.162	70	-0.018	0.045

Table 3.7 DFBETAS for Model II

Hospital ID	DFBETAS Transplant Rate	DFBETAS Infection Rate	DFBETAS LOS	Hospital ID	DFBETAS Transplant Rate	DFBETAS Infection Rate	DFBETAS LOS
1	-0.068	-0.151	0.086	36	0.030	0.093	-0.036
2	0.082	0.110	-0.048	37	-0.021	0.008	0.011
3	-0.074	0.033	0.022	38	-0.048	-0.007	0.063
4	-0.178	-0.083	**0.439**	39	-0.042	-0.099	0.093
5	-0.042	0.010	0.112	40	0.031	0.077	-0.050
6	0.099	0.070	0.061	41	0.052	0.049	-0.043
7	0.036	-0.055	0.019	42	0.039	-0.003	-0.061
8	-0.059	0.084	0.000	43	-0.012	0.006	-0.006
9	-0.112	-0.041	-0.057	44	-0.043	-0.026	-0.002
10	0.007	-0.008	-0.008	45	-0.098	-0.159	0.145
11	-0.014	-0.068	0.009	46	0.098	0.000	-0.073
12	-0.057	-0.007	0.018	47	0.104	0.003	-0.048
13	0.070	-0.200	0.011	48	-0.063	**-0.736**	**-0.378**
14	-0.029	0.051	-0.022	49	0.086	0.039	0.046
15	-0.110	-0.041	0.041	50	-0.003	-0.021	0.034
16	-0.013	0.054	0.040	51	-0.046	0.087	-0.067
17	-0.072	0.056	0.004	52	-0.059	-0.029	0.077
18	0.028	0.061	-0.070	53	-0.032	0.010	0.074
19	0.099	0.040	-0.095	54	-0.185	0.081	-0.027
20	**-0.596**	0.019	0.189	55	-0.134	-0.162	0.193
21	-0.074	-0.007	-0.017	56	-0.021	0.001	0.045
22	0.101	0.213	-0.192	57	0.002	0.025	-0.049
23	-0.005	0.029	-0.023	58	0.000	0.000	-0.001
24	0.109	0.034	-0.100	59	**0.310**	**0.248**	**-0.306**
25	-0.031	-0.089	0.063	60	-0.009	0.012	-0.006
26	**-0.353**	**-0.245**	0.111	61	-0.027	-0.004	-0.033
27	-0.107	0.174	**0.376**	62	0.041	-0.026	-0.002
28	**0.808**	-0.123	**0.340**	63	0.003	0.000	0.014
29	**0.650**	0.063	**-0.688**	64	0.072	-0.018	-0.039
30	-0.025	-0.004	0.049	65	-0.010	-0.006	0.009
31	0.070	0.134	-0.110	66	-0.035	0.013	0.061
32	0.009	0.015	-0.002	67	-0.030	0.131	-0.139
33	-0.003	-0.077	0.047	68	-0.009	0.067	-0.093
34	-0.037	-0.012	0.030	69	0.036	-0.058	-0.047
35	0.007	0.072	0.025	70	0.007	0.064	-0.055

(iii) *Influence on the Performance (COVRATIO)*

The DFFITS and DFBETAS diagnostics highlight those data points whose presence in the analysis bears a noticeable influence on the regression results. However, they do not indicate whether this influence is favorable or detrimental. One can gain insight into model performance by examining the variance-covariance matrix of the parameter estimates given by Equation 3.29. The determinant of this matrix is known as the *generalized variance* (GV)

$$\mathrm{GV} = \det\left[\sigma^2(\mathrm{X}'\mathrm{X})^{-1}\right] \tag{3.31}$$

The ratio of GV of the model that is fitted after removing the i^{th} data point to GV of the model fitted with the i^{th} data point included is called COVRATIO. The estimators $\hat{\sigma}_{-i}$ and $\hat{\sigma}^2$ are used instead of σ^2 in the numerator and denominator, respectively. Then, the i^{th} COVRATIO is given by

$$(\mathrm{COVRATIO})_i = \frac{\det\left[\hat{\sigma}^2_{-i}(\mathrm{X}'_{-i}\mathrm{X}_{-i})^{-1}\right]}{\det\left[\hat{\sigma}^2(\mathrm{X}'\mathrm{X})^{-1}\right]} \tag{3.32}$$

where X_{-i} denotes the $(n-1)\times p$ data matrix with the i^{th} data point (row) removed. Since smaller GV values indicate higher precision in the estimation of the parameters, then a $(\mathrm{COVRATIO})_{-i} > 1$ implies that the presence of the i^{th} data point in the model is favorable as it reduces GV.

Conversely, a $(\text{COVRATIO})_{-i} < 1$ implies that the presence of the i^{th} data point in the model is detrimental as it increases GV.

A computational form of COVRATIO is given by

$$(\text{COVRATIO})_i = \left(\frac{\hat{\sigma}^2_{-i}}{\hat{\sigma}^2}\right)^p \left(\frac{1}{1-h_{ii}}\right) \tag{3.33}$$

The term $1/1\text{-}h_{ii}$ in the above Equation 3.33 is the ratio of $\det[(\mathrm{X}'\mathrm{X})^{-1}]$ to $\det[(\mathrm{X}'_{-i}\mathrm{X}_{-i})^{-1}]$. If the i^{th} data point is a high leverage point ($h_{ii} \cong 1$) then it will yield a large $(\text{COVRATIO})_i$ which indicates that the i^{th} data point has a favorable effect on the precision of the parameter estimates, assuming that the point is not an outlier in the y direction. If the i^{th} data point is, in fact, an outlier then $(\hat{\sigma}^2_{-i}/\hat{\sigma}^2)^p$ will be less than one by a considerable margin. Thus, similar to DFFITS and DFBETAS, the combination of leverage (distance of the data point from the center of the x space) and outlier status (error in y direction) work hand in hand to create the diagnostic criterion. A yardstick is to consider the i^{th} data point as having a positive impact on the regression if $(\text{COVRATIO})_i > 1+\frac{3p}{n}$ while $(\text{COVRATIO})_i < 1-\frac{3p}{n}$ indicates that the i^{th} data point has a negative impact on the regression [97]. Applying this yardstick to Model I, the i^{th} data point was deemed to be favorable if $(\text{COVRATIO})_i > 1.129$ while it was deemed to be detrimental if $(\text{COVRATIO})_i < 0.871$. For Model II, the corresponding cut-off points were 1.171 and 0.829,

respectively. The $(COVRATIO)_i$ values of the two models are plotted against the predicted values in Figure 3.10. As illustrated in the figure, $(COVRATIO)_i$ of Hospitals #4, #26, and #29 falls below the low cut-off point in both models and these hospitals are therefore considered to have a potentially detrimental impact on the two models. However, in order to put things in perspective, it is important to note that COVRATIO should be taken in context with DFFITS, DFBETAS, outlier status and leverage. With the exception of Hospital #4 in Model II, these hospitals were identified by both DFFITS and DFBETAS in the two models. Moreover, all three hospitals that were labeled as "bad" by COVRATIO in the two models were also identified as outliers in both models. This is not surprising since by definition, an outlier is a data point with a large residual and the presence of such a data point in the model will increase variance ($\hat{\sigma}^2$) causing the $(\hat{\sigma}^2_{-i}/\hat{\sigma}^2)^p$ ratio in Equation 3.33, and ultimately $(COVRATIO)_i$, to fall considerably below 1. In general, outlier data points that have low leverage (small h_{ii}) produce a $(COVRATIO)_i$ well below one which indicates that they decrease the precision of the parameter estimates.

Figure 3.10 also reveals that $(COVRATIO)_i$ for Hospitals #35 and #48 falls above the upper cut-off point in both models, $(COVRATIO)_i$ for Hospitals #12, #20, #28 and #54 surpasses this point in Model I only, and $(COVRATIO)_i$ for Hospital #68 exceeds this cut-off in Model II only. Recall that, with the exception of Hospitals #12 and #68, these hospitals were

previously determined to be high leverage points. Hospitals #20 and #28 in Model I, in addition to Hospital #48 in both models, were highlighted by DFFITS and DFBETAS. These diagnostics did not highlight any of the other hospitals that were labeled as being "good" by COVRATIO in either model. However, this does not necessarily imply that these non-highlighted hospitals are "inert". These data points may impact hypothesis testing and the conclusions drawn from the analysis by virtue of their favorable impact on the precision of the parameter estimates as indicated by their large $(\text{COVRATIO})_i$. In general, data points that have high leverage (large h_{ii}) but are not outliers produce a $(\text{COVRATIO})_i$ well above one which indicates that they increase the precision of the parameter estimates. Such high leverage points will cause the term $(1/1-h_{ii})$ in Equation 3.33, and ultimately $(\text{COVRATIO})_i$, to be considerably higher than one.

As previously mentioned, Hospital #28 was identified as a high influence point in Model I. The reason why its $(\text{COVRATIO})_i$ is larger than one is because its "outlier-ness", which pulls $(\text{COVRATIO})_i$ down, is outweighed by its high leverage, which pushes $(\text{COVRATIO})_i$ up. Thus, the magnitude of COVRATIO and its direction, above or below unity, is determined by the extent by which one of the two opposing forces, leverage and outlierness, outweighs the other. In Model II, $(\text{COVRATIO})_i$ for Hospitals #20 and #28, among others, does not exceed the upper cut-off point as

shown in Figure 3.10. However, such hospitals should be examined closely since were highlighted by both DFFITS and DFBETAS.

The analysis of residuals and influence diagnostics play an important role in determining whether the model is being dictated by a few suspect data points. One can predict the impact of suspect data points on the model by determining their status as outliers, high leverage points or high influence points. On the other hand, influence diagnostics determine the exact impact of such suspect data points. An unexpected magnitude or sign of a parameter estimate may be due to the effect of a few suspect data points. Inspection of DFBETAS pinpoints the data points implicated in such scenarios. COVRATIO is a measure of the precision of the parameter estimates and the presence of extreme $(COVRATIO)_i$ values in either direction may change the significance of parameter estimates and may consequently affect our model selection. Finally, the presence of a set of outliers or high influence points may indicate the need to apply a transformation on the outcome variable or even consider a different model altogether.

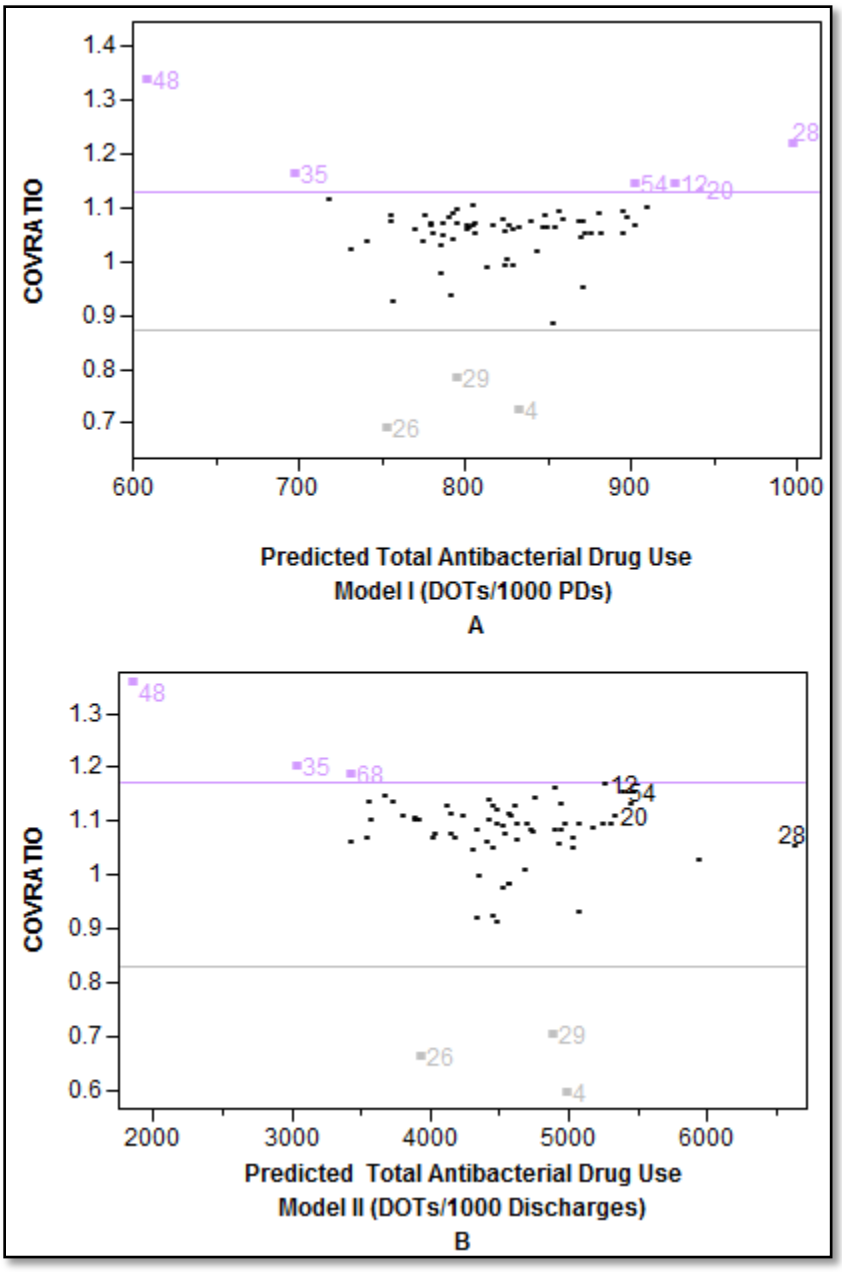


Figure 3.10 Plots of COVRATIO versus predicted total antibacterial drug consumption for Model I (Figure A) and Model II (Figure B). The horizontal violet lines represent the $\mathbf{1} + \frac{3p}{n}$ cut-off point above which data points are considered to have a favorable impact on the model (violet data points). The horizontal gray lines represent the $\mathbf{1} - \frac{3p}{n}$ cut-off point below which data points are considered to have detrimental effect on the model (gray data points). As explained in the text, COVRATIO should be taken in the context of other the other influence diagnostics to be meaningful.

3.2.7 Checking Model Assumptions

The popularity of OLS is largely attributed to the attractive properties of the OLS estimators. According to the *Gauss-Markov Theorem*, OLS estimators are *Best Linear Unbiased Estimators* (BLUE). Here "best" means that OLS estimators are efficient in the sense of having the least variance among all linear unbiased estimators. However, this desirable property holds only when the assumptions underlying OLS are satisfied. Therefore, checking the following assumptions should ideally be carried out whenever a linear regression model is fitted.

(i) *Linearity*

As the name linear regression implies, the outcome variable is assumed to be a linear function of the predictor variable(s). If one fits a linear regression model when the functional form of the relationship is in fact non-linear, then the OLS estimates will no longer be unbiased. The linearity assumption can be checked graphically by inspecting the bivariate scatterplots in Figure 3.4 and/or the residual (studentized residual) by predicted plots such as the ones depicted in Figure 3.6. One would typically look for any nonlinear trends such as curvilinear patterns when inspecting such plots. Neither graph shows any non-linear patterns so the linearity assumption seems to hold here for both Model I or Model II.

(ii) *Homoscedasticity (constant variance)*

As previously mentioned, the errors are assumed to have the same variance regardless of the value of the *x*'s. This assumption is also known as *homoscedasticity* which is Greek for "same variance". If this assumption is violated, then the OLS estimators will still be unbiased but they are no longer efficient (do not have the minimum variance among all linear unbiased estimators).

The homoscedasticity assumption is usually checked graphically by examining the residual (studentized residual) by predicted plots such as the ones displayed in Figure 3.6. The plots should ideally reveal a random scattering around 0 (the horizontal black line in the figure) with no particular pattern. The random scattering is evident in the figure but probably to a greater degree in Figure 3.6 A (Model I) than Figure 3.6 B (Model II). However, one should relatively be comfortable that the homoscedasticity assumption holds for both models.

(iii) *Independence*

The independence assumption refers to the lack of dependence between the error terms and, consequently, the *y* values. In other words, there should be no autocorrelation between the errors for this assumption to be satisfied. In the presence of autocorrelation, the OLS estimates will remain unbiased but they are no longer efficient. Autocorrelation usually leads to

underestimating the standard errors of the parameter estimates and, consequently, inflating the Type I error.

The independence assumption can be verified either graphically or by formal statistical tests. However, this is not usually done unless one has reason to suspect that autocorrelation may have been introduced by the methods used in sampling or collecting the data. Also, autocorrelation is usually present to an appreciable extent in certain types of data such as time series and clustered data. Since there is no reason to believe that the consumption of antibacterial drugs in one hospital may be dependent on that of another, the independence assumption is assumed to be satisfied for the two models.

(iv) *Normality*

The three assumptions above are necessary for the OLS estimators to be BLUE. On the other hand, normality of the errors need not be assumed to achieve this desirable property. Nonetheless, the normality assumption is required for performing inferential statistics since both the t-test and F-test assume normality. Moreover, if the normality assumption is satisfied (in addition to the assumptions of linearity, homoscedasticity, and independence), the OLS estimators will have enhanced properties since they become *Uniformly Minimum-Variance Unbiased Estimators* (UMVUE). That is, OLS estimators will have minimum variance among all unbiased estimators, not just the linear ones.

If the normality assumption is satisfied, a histogram of the raw residuals or, preferably, the studentized residuals would reasonably assume the "bell-shaped" curve that is typical of the normal distribution. Q-Q plots (also known as normal quantile plots) are another graphical method for checking the normality assumption. A Q-Q plot can be constructed by plotting the studentized residuals on one axis and the corresponding expected *z*-scores (normal quantiles) from the standard normal distribution on the other. If the data were perfectly normally distributed, then the data points of the Q-Q plot would perfectly fall along a 45-degree diagonal line. Conversely, if the point pattern of a Q-Q plot exhibits considerable curvature that strays away from the perfect linear fit, this would indicate a marked departure from normality. The histograms of the studentized residuals with overlaid normal density curves are displayed along with the Q-Q plots for Model I and Model II in Figure 3.11. For both models, the histograms appear to be reasonably symmetric and follow the normal density curves fairly closely while the data points in the Q-Q plots do not appear to deviate extensively from the 45-degree diagonal line representing perfectly normally distributed data. Therefore, it is probably safe to assume normality in both models. Since the assumptions of linear regression were met, no consideration was given to Poisson regression.

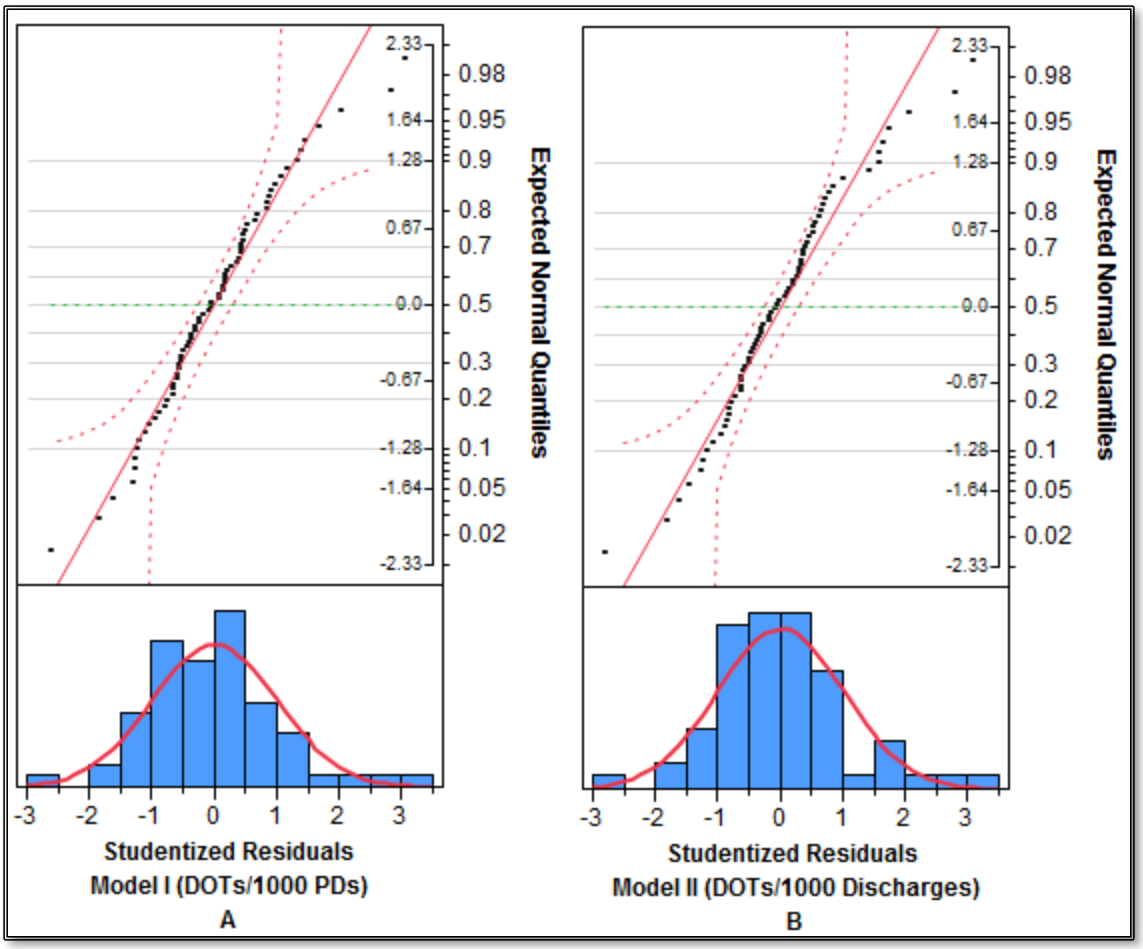


Figure 3.11 Normal quantile plots (upper panel) and histograms with overlain normal density curves (lower panel) of the studentized residuals obtained from Model I (Figure A) and Model II (Figure B). The two histograms appear reasonably symmetric and follow the overlaid normal density curves fairly closely. The red solid diagonal lines in the Q-Q plots represent the ideal path data would follow if it were perfectly normal. Since data do not deviate markedly from this ideal line and do not cross the dashed red lines, then one can conclude that there are no serious departures from normality in either model.

3.2.8 **Model Validation**

(i) *Internal Validation*

Model validation is an important guard against overfitting the model to the study sample. One of the objectives of model validation is to evaluate the usefulness of a given model in predicting the outcome of future observations. R^2 is a goodness-of-fit statistic and a high R^2 does not necessarily imply that the model will be useful for prediction purposes. While the R^2 quantifies the proportion of the variability in the outcome variable explained by the model using the *existing* dataset, the predicted R^2 , on the other hand, measures the proportion of the variability in the outcome variable the model is expected to explain when it is fitted to a *new* dataset (i.e., new observations). Thus, unlike the "ordinary" R^2, the predicted R^2 is useful for model validation purposes as it provides a useful insight into the predictive capabilities of a model.

The predicted R^2 is obtained by the LOOCV method which is identical to the previously described method of obtaining the PRESS statistic. The predicted R^2 is given by

$$R^2_{PRED} = 1 - \frac{\text{PRESS}}{\text{SST}} \tag{3.34}$$

Since SST is constant for any given dataset, then Equation 3.34 implies that the model with the smallest PRESS will also have the largest predicted R^2.

The candidate models selected to represent Model I and Model II (Model IA and Model IIA in Table 3.3) had the highest predicted R^2 among all competing models. The predicted R^2 for the two models, in the above order, is 0.25 and 0.58 which is in reasonable agreement with the adjusted R^2 of 0.29 and 0.63, respectively. This indicates that neither model was overfit.

LOOCV is a resource intensive procedure but it is often superior to the simpler and more commonly used "hold-out cross validation" which splits the sample into a training set and a testing set. This is especially true when the sample size is small like the one in this study since the latter method wastes valuable data and may result in imprecise and biased parameter estimates [98]. However, while LOOCV produces approximately unbiased prediction errors, it may also have very high variance and may consequently select the "wrong" model [99].

(ii) *External Validation*

External validation should ideally be carried out using a validation set that is independent of the calibration set. However, most studies, including this one, do not have the luxury of having a completely independent dataset for validation. The validation set consisted of n= 55 hospitals that are a subset of the n= 70 hospitals composing the calibration set but whereas the data used in the latter was from 2009, the one used in the former was from the 2008 calendar year. The validation adjusted R^2 for model I was 0.25 while that for Model II was 0.57. These were in agreement with both the

corresponding adjusted R^2 for the two models and the corresponding predicted R^2 obtained from the internal validation method. In line with the previous conclusion from internal validation, the external validation results indicate that neither model was overfit. The internal and external validation scatterplots are displayed in Figure 3.12.

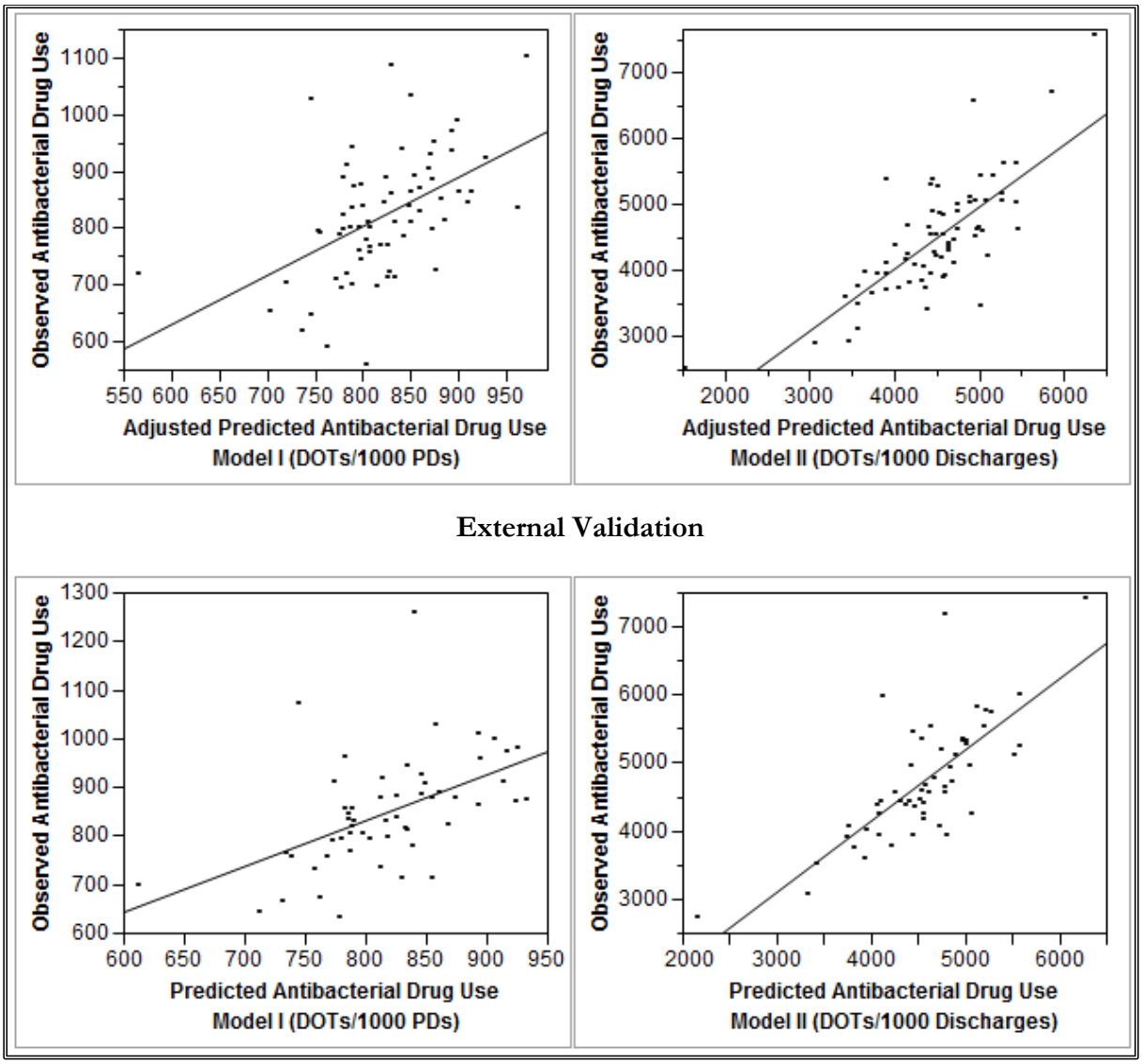


Figure 3.12 Observed by predicted plots representing internal (upper panel) and external (lower panel) validation methods. Internal validation used the original calibration set to perform the *leave-one-out cross validation* (LOOCV) method and consequently obtain the adjusted predicted values and the predicted R^2 (R^2_{PRED}= 0.25 for Model I and 0.58 for Model II). In external validation, the prediction equations of the two models were applied to the validation set (see text for details on validation set) to derive the corresponding predicted values, which were in turn plotted against the corresponding observed values of the validation set and the validation adjusted R^2 were obtained (R^2_{ADJ}= 0.25 for Model I and 0.57 for Model II). The results of both internal and external validation methods do not suggest that either model was overfit.

Chapter IV
The Application of Standardization Methods to the Risk-adjustment of Antibacterial Drug Use

4.1 Methods

4.1.1 Data Source and Assignment of Patients to Clinical Service Lines

A second dataset was provided by UHC where adult discharges in each of the 70 hospitals that subscribed to the CRM database during 2009 (section 3.1) were stratified into 35 distinct categories. The UHC assigned adult patients in each hospital to 1 of these categories, which hereinafter will be referred to as clinical service lines (CSLs) and are listed in Table 4.1. This classification of patients into CSLs is based on their assignment to 1 of 745 MS-DRGs by the CMS MS-DRG Grouper software upon discharge (http://www.ntis.gov/products/grouper.aspx; accessed on 16 January 2012). The software classifies patients into groups (MS-DRGs) expected to have similar hospital resource utilization based upon primary and secondary diagnoses, procedures, the presence of complications and comorbidities, demographics and discharge status [44]. The grouping of patients into CSLs was based upon the similarity and relatedness of their

clinical conditions as determined by their MS-DRG assignment. The complete MS-DRG composition of the 35 CSLs can be found in Table A3 in the appendix. The CSLs assumed the role of the strata in the standardization procedures and the CSL-specific AbC rates and weights were used to derive the standardized hospital-wide rates as will be explained shortly.

4.1.2 Data Components and Descriptive Statistics

The following variables were available in the dataset within each CSL for each hospital: the number of discharges, the number of discharges receiving (at least one dose of) antibacterial drug therapy, the number of patient days, the number of DOTs and the number of LOT. These variables were pooled across the entire sample of 70 hospitals to create the reference population. However, since the CSL composition varied from one hospital to another (i.e., not all hospitals had all 35 CSLs), it was not possible to standardize all hospitals to a common reference population and a different reference population was created for each set of hospitals that had the same CSL composition (see page 117 for further details).

In both individual hospitals as well as the reference population, the above mentioned variables were used to calculate the CSL-specific AbC rate in DOTs/1000 discharges and DOTs/1000 patient days; in addition to the different components of these measures, including LOT/discharge for patients receiving antibacterial therapy, proportion of discharges receiving antibacterial therapy, DOTs/LOT ratio and mean LOS. For the sake of

brevity and clarity, I will henceforth refer to the discharges receiving antibacterial drug therapy as “cases” while the term “discharges” will be used to refer to all discharged patients irrespective of whether or not they received antibacterial therapy. The data were summarized using the mean and median as measures of central tendency while the range was used as the measure of dispersion.

4.1.3 The Application of Direct and Indirect Standardization Procedures

The Direct Standardization Procedure

For each hospital, the CSL-specific AbC rate (DOTs/discharge) within each CSL was multiplied by the number of discharges in the corresponding CSL of the reference population to yield the expected number of DOTs in that CSL. These expected CSL-specific number of DOTs were summed across all the CSLs that compose the given hospital to give the expected hospital-wide total number of DOTs in the reference population. The DSR, or the expected (i.e., adjusted) hospital-wide AbC rate measured in DOTs/1000 discharges was obtained by dividing the expected hospital-wide total number of DOTs by the total number of discharges in the corresponding reference population and multiplying the result by 1000. The hospital-wide E/O ratio for a given hospital was calculated by dividing its DSR by the crude (i.e., observed) rate of its corresponding reference population.

The direct standardization procedure was also applied to derive the standardized values of the four components of AbC rates mentioned in

section 4.1.2. Specifically, the expected hospital-wide DOTs/LOT ratio was obtained by dividing the expected hospital-wide total number of DOTs by the expected hospital-wide total number of LOT. The latter was derived through direct standardization in a similar manner to the former. Similarly, the direct standardization procedure was also used to calculate the expected hospital-wide total number of cases using the CSL-specific proportion of cases in the study hospitals and the number of discharges in the corresponding CSLs of the reference population. The expected hospital-wide total number of cases was divided by the total number of discharges in the corresponding reference population to yield the expected hospital-wide proportion of cases. Moreover, the expected hospital-wide LOT/case was obtained by dividing the expected hospital-wide total number of LOT by the expected hospital-wide total number of cases.

Finally, the expected hospital-wide mean LOS was calculated by dividing the expected hospital-wide total number of patient days by the total number of discharges in the corresponding reference population. The numerator was obtained through direct standardization using the CSL-specific mean LOS in the study populations and the number of discharges in the corresponding CSLs of the reference population.

The Indirect Standardization Procedure

The indirect standardization procedure is a mirror image of its direct counterpart. That is, for each hospital, the CSL-specific DOTs/discharge rate within each CSL of the corresponding reference population was

multiplied by the number of discharges in the corresponding CSL of the given hospital to yield the expected number of DOTs in that CSL. These expected CSL-specific number of DOTs were summed across all the CSLs that compose the given hospital to give the expected hospital-wide total number of DOTs for that hospital. The expected hospital wide DOTs/1000 discharges rate was obtained by dividing the expected hospital-wide total number of DOTs for the hospital by its total number of discharges and multiplying the result by 1000.

The hospital-wide O/E ratio for a given hospital was calculated by dividing its observed rate by its expected one. An O/E ratio was also calculated for each of the four components of AbC rates. The expected hospital-wide values of these components were calculated as described in the direct standardization procedure but by applying indirect standardization instead of direct standardization. Finally, the ISR was calculated by multiplying the O/E ratio for the DOTs/1000 discharges rate by the crude rate in the corresponding reference population.

Identifying Outliers for Both Standardization Procedures

In order to identify outliers, I first calculated *z*-scores by subtracting the E/O (O/E) ratio of each hospital from the mean E/O (O/E) ratio of the entire study population and subsequently dividing by the corresponding standard deviation. I then classified hospitals as high or low outliers at the 95% confidence level if their *z*-score was higher than +1.96 or lower than

-1.96, respectively. On the other hand, hospitals were classified as high or low outliers at the 90% confidence level if their z-score was higher than +1.64 and lower than -1.64, respectively.

4.1.4 Comparison of Antibacterial Drug Consumption Measures and Risk-adjustment Methods

In the direct and indirect standardization procedures, hospitals were ranked according to their E/O and O/E ratios, respectively, while in the MLR models, hospitals were ranked based on their R-student statistic. The weighted kappa coefficient (weighted κ) was used to compare the extent of agreement of direct standardization with indirect standardization, Model I with Model II and Model II with either standardization procedure with respect to ranking hospitals. The weighted κ coefficients were obtained using the PROC FREQ procedure in SAS. The guidelines proposed by Altman were used to interpret the κ scores [100]. The agreement between the different methods with respect to the hospitals they identified as outliers was also described.

4.1.5 Comparison of Interhospital Antibacterial consumption at the CSL Level

A direct comparison of the observed CSL-specific AbC rates and their components between hospitals was carried out. Weighted κ was also used to measure the extent of agreement between the CSL-specific DOTs/1000 discharges and DOTs/1000 PDs rates in ranking hospitals.

4.2 Results

4.2.1 Descriptive Statistics

Demographics by Clinical Service Line

Table 4.1 provides the summary statistics for the number of discharges, the number of patient-days and LOS stratified by CSL. The general medicine CSL had both the largest number of discharged patients (median, 5099; range, 232-12,800) and the largest number of patient-days (median, 21,693; range, 933-69,761) accounting for 21.1% of the 1,791,172 total discharges and 16.9% of the 9,820,959 total patient-days. Other CSLs with appreciable size included obstetrics which accounted for 11.5% of the total number of discharges (median, 2710; range, 6-8668) and 6.6% of the total number of patient-days (median, 8493; range, 16-30,227), cardiology which accounted for 10% of the total number of discharges (median, 2267; range, 46-6333) and 7.6% of the total number of patient-days (median, 8688; range, 152-29,214) and general surgery which accounted for 8.2% of the total number of discharges (median, 1895; range, 94-6703) and 10.7% of the total number of patient-days (median, 14,021; range, 576-44,396).

At the opposite end, the transplant CSLs in general had some of the smallest sizes. For example, the heart transplant/implant of heart assist system CSL accounted for only 0.10% of the total number of discharges (median, 30; range, 1-113) and only 0.70% of the total number of patient-days (median, 1009; range, 2-7887), whereas the BMT CSL accounted for only 0.28% of the total number of discharges (median, 88; range, 1-453) and

only 1.14% of the total number of patient-days (median, 1972; range, 1-8405). However, unlike the aforementioned large size CSLs, the transplant CSLs were among the CSLs not represented at every hospital (Table 4.1). The two transplant CSLs, in the above order, had a mean LOS of 32.5 days and 23.5 days. The other CSL with a notably long LOS was the ventilator support (mean, 30.7 days) while the gynecology (mean, 2.7 days) and the obstetrics (mean, 3.2 days) CSLs had the shortest LOS.

Aggregated Antibacterial Drug Consumption by Clinical Service Line

Table 4.2 summarizes different measures of total aggregate AbC stratified by CSL. When AbC was measured in DOTs/1000 PDs, the lung transplant CSL had the highest consumption (mean, 2039; range, 933-2967) followed by the Human Immunodeficiency Virus (HIV) CSL (mean, 1704; range, 705-2533) whereas the psychiatry CSL had the lowest consumption (mean, 97; range, 29-488). When AbC was measured in DOTs/1000 discharges, the ventilator support CSL had the highest consumption (mean, 38,874; range, 18,333-71,979) followed by the heart transplant/implant of heart assist system CSL (mean, 35,928; range, 2000-71,156) and the lung transplant CSL (mean, 34,753; range, 13,067-75,545) whereas the psychiatry CSL had the lowest consumption (mean, 824; range, 190-3108).

The other variables in Table 4.2 measure different meaningful components of AbC. LOT/case is a proxy measure of the average duration of therapy per treated patient while the DOT/LOT ratio is a proxy measure of

the average number of administered antibacterial drugs. The product of these two variables is DOTs/case. LOT/1000 PDs may be considered a proxy measure of the average percentage patient days that are treatment days (i.e., a patient day where at least one dose of an antibacterial drug is administered).

The components of AbC are somewhat obscured by the DOTs/1000 PDs and DOTs/1000 discharges measures. However, the two measures can be decomposed and expressed as a function of these components. More specifically, the DOTs/1000 discharges measure is the product of the DOTs/LOT ratio and LOT/1000 discharges.

$$\frac{no.of\ DOTs}{no.of\ discharges} = \frac{no.\ of\ DOTs}{no.\ of\ LOT} \times \frac{no.\ of\ LOT}{no.\ of\ discharges} \tag{4.1}$$

Since LOT/1000 discharges is the product of LOT/1000 cases and the percentage of cases (discharges receiving antibacterial therapy), Equation 4.1 can be rewritten as

$$\frac{no.\ of\ DOTs}{no.\ of\ discharges} = \frac{no.\ of\ DOTs}{no.\ of\ LOT} \times \frac{no.\ of\ LOT}{no.\ of\ cases} \times \frac{no.\ of\ cases}{no.\ of\ discharges} \tag{4.2}$$

$$\frac{DOTs}{discharge} \qquad \frac{DOTs}{LOT}\ ratio \qquad \frac{LOT}{case} \qquad percent\ discharges\ receiving\ antibiotics$$

DOTs/1000 PDs, on the other hand, is the product of the DOTs/LOT ratio and LOT/1000 PDs.

$$\frac{no.of\ DOTs}{no.of\ patient\ days} = \frac{no.of\ DOTs}{no.of\ LOT} \times \frac{no.of\ LOT}{no.of\ patient\ days} \tag{4.3}$$

Dividing both numerator and denominator of the last term by the number of discharges

$$\frac{no.of\ DOTs}{no.of\ patient\ days} = \frac{no.of\ DOTs}{no.of\ LOT} \times \frac{no.of\ LOT / no.of\ discharges}{no.of\ patient\ days / no.of\ discharges}$$

Thus, in analogy to Equation 4.2, the above equation can be rewritten as

$$\frac{no.of\ DOTs}{no.of\ patient\ days} = \frac{no.of\ DOTs}{no.of\ LOT} \times \frac{\frac{no.of\ LOT}{no.of\ cases} \times \frac{no.of\ cases}{no.of\ discharges}}{no.of\ patient\ days / no.of\ discharges} \tag{4.4}$$

$\frac{DOTs}{patient\ day}$ $\frac{DOTs}{LOT}$ ratio $\frac{LOT}{case}$ LOS *percent discharges receiving antibiotics*

A comparison of Equation 4.4 with Equation 4.2 reveals that the percent discharges receiving antibiotics, LOT/case and DOTs/LOT ratio are components that are common to both the DOTs/1000 discharges and DOTs/1000 PDs measures. This comparison also reveals the well-known fact that the latter measure equals the former divided by the average LOS.

Figure 4.1 shows AbC displayed in ascending order and measured in both DOTs/1000 discharges (upper panel) and DOTs/1000 PDs (lower

panel), along with the above-mentioned components, in 5 CSLs with different consumption patterns. As expected, the upper panel shows that as the DOTs/1000 discharges measure increases, the three components that compose it also exhibit a general increasing trend. However, as shown in the lower panel, this linear pattern between these components and AbC was clearly absent when the latter was measured in DOTs/1000 PDs. This is especially true for the LOT/case component and, to a lesser extent, the percent number of cases component.

The figure, as well as Table 4.2, also reveals that the two AbC rates were concordant within the lung transplant, gastroenterology and psychiatry CSLs as they had very high, average and very low use, respectively, in both rates. Conversely, the two measures were discordant within the heart transplant/implant of heart assist system and, to a lesser extent, the ophthalmology CSLs. As reported in Table 4.2 and illustrated in Figure 4.1, the former had a very high use in DOTs/1000 discharges (mean, 35,928) but only a moderate use in DOTs/1000 PDs (mean, 912) while the latter had a relatively low use in DOTs/100 discharges (mean, 3,664) but a relatively high use in DOTs/1000 PDs (mean, 1,112). The two CSLs, in the above order, had a mean percent discharges receiving antibiotics of 99% and 69.8%, a mean LOT/case of 21.6 days and 3.3 days, a mean DOTs/LOT ratio of 1.68 and 1.57 and a mean LOS of 39.4 days and 3.3 days.

The discrepancy between the two measures within the two CSLs is attributed to LOS since it is a component of the DOTs/1000 PDs but not the DOTs/1000 discharges measure while the other 3 components are common to both measures as previously indicated. It is clear that this paradoxical situation was caused by the extremely long LOS in the first CSL and the extremely short one in the second resulting in a disproportionate deflation and inflation, respectively, of the DOTs/1000 PDs measure relative to the DOTs/1000 discharges measure. This disproportionate effect of LOS was also reflected in the LOT/1000 PDs measure which was moderate for the first CSL (mean, 544) and relatively high for the second (mean, 708).

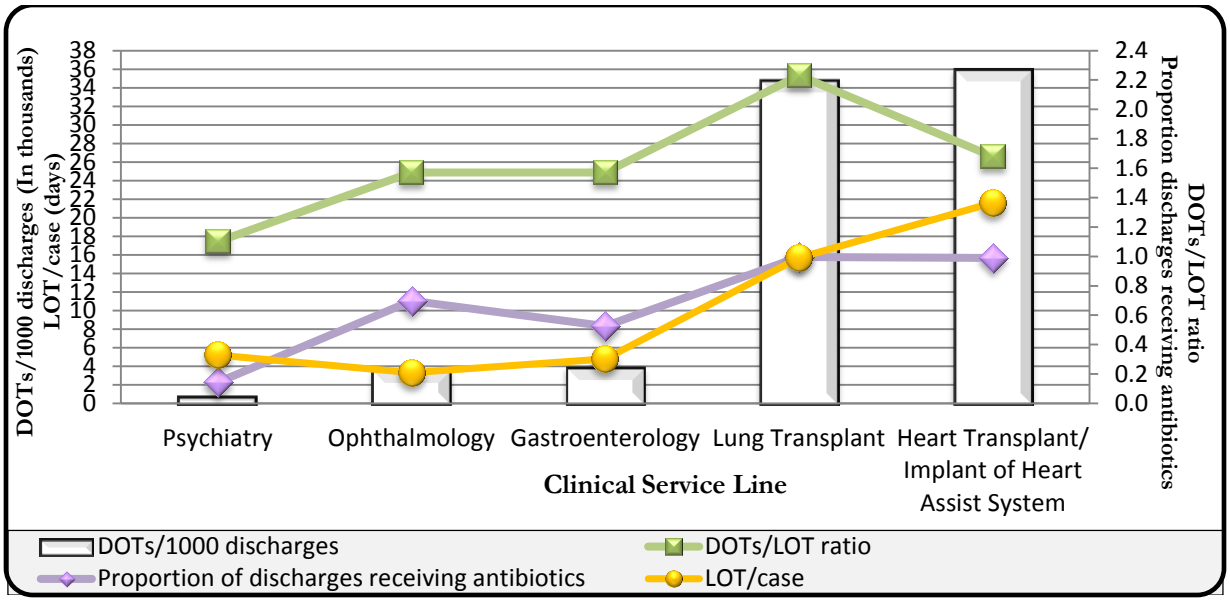
Table 4.1 Characteristics of Adult Discharges at 70 U.S. Academic Medical Centers in 2009 Stratified by Clinical Service Line

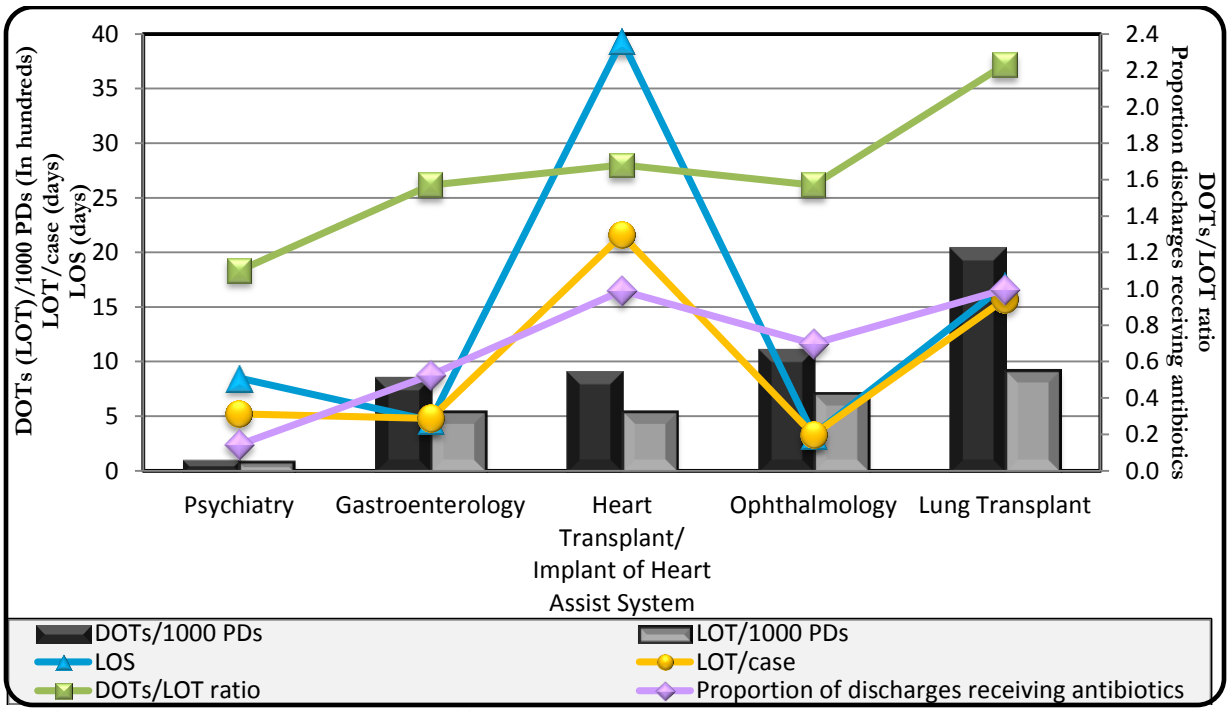
			No. of discharges						No. of patient days						Length of stay			
CSL ID	CSL Description	N	Sum	% of Total	Mean	Median	Min	Max	Sum	% of Total	Mean	Median	Min	Max	Mean	SD	Min	Max
1	Bone Marrow Transplant	50	5014	0.28%	100	88	1	453	112030	1.14%	2241	1972	1	8405	22.3	6.80	1.0	44.2
2	Burns	66	4945	0.28%	75	10	1	445	43445	0.44%	658	99	1	4395	8.8	3.49	1.0	16.3
3	Cardiology	70	178678	9.98%	2553	2267	46	6333	748276	7.62%	10690	8688	152	29214	4.2	0.64	2.9	5.9
4	Cardiothoracic Surgery	70	59619	3.33%	852	688	5	3412	521190	5.31%	7446	5492	32	24264	8.7	1.70	6.1	16.8
5	Dental/Oral Surgery	69	3307	0.18%	48	42	9	221	11079	0.11%	161	140	28	480	3.4	1.08	1.4	8.3
6	Dermatology	69	3473	0.19%	50	42	11	194	15351	0.16%	222	181	39	888	4.4	0.93	2.8	6.8
7	Gastroenterology	70	126928	7.09%	1813	1738	71	4828	588163	5.99%	8402	7788	308	21203	4.6	0.48	3.6	5.8
8	Gynecology	70	30453	1.70%	435	399	19	1246	79471	0.81%	1135	1043	46	3303	2.6	0.47	1.3	3.9
9	Heart Transplant/ Implant of Heart Assist System	51	1756	0.10%	34	30	1	113	69171	0.70%	1356	1009	2	7887	39.4	16.63	2.0	74.2
10	HIV	69	8421	0.47%	122	72	5	1194	73535	0.75%	1066	685	27	10521	8.7	3.25	3.9	24.2
11	Kidney/Pancreas Transplant	59	6285	0.35%	107	87	13	284	46100	0.47%	781	633	110	3365	7.3	2.09	3.8	14.3
12	Liver Transplant	46	2396	0.13%	52	48	6	163	40782	0.42%	887	724	73	4679	17	4.85	7.9	28.7
13	Lung Transplant	30	687	0.04%	23	15	2	70	11710	0.12%	390	309	30	1216	17	4.63	9.5	28.9
14	Medical Oncology	70	62416	3.48%	892	804	6	2417	415843	4.23%	5941	5103	27	17278	6.7	1.19	4.2	9.6
15	Medicine General	70	378417	21.13%	5406	5099	232	12800	1663899	16.94%	23770	21693	933	69761	4.4	0.54	3.1	5.8
16	Neurology	70	98160	5.48%	1402	1303	31	3232	433657	4.42%	6195	5625	150	14033	4.4	0.61	3.0	6.4
17	Neurosurgery	70	37203	2.08%	531	454	1	1451	269137	2.74%	3845	3373	5	11483	7.2	2.14	4.5	17.3
18	Obstetrics	70	206121	11.51%	2945	2710	6	8668	646232	6.58%	9232	8493	16	30227	3.1	0.45	2.1	4.6
19	Ophthalmology	69	4199	0.23%	61	42	7	570	13838	0.14%	201	152	24	1159	3.3	0.92	2.0	6.5
20	Orthopedics	70	111418	6.22%	1592	1337	363	5705	483740	4.93%	6911	6189	2087	23177	4.3	0.76	3.1	6.3
21	Otolaryngology	70	17110	0.96%	244	207	7	862	79645	0.81%	1138	1033	18	2745	4.7	0.98	2.6	8.0
22	Plastic Surgery	70	10778	0.60%	154	138	6	520	105930	1.08%	1513	1337	63	5382	9.8	2.87	5.8	21.8
23	Psychiatry	69	57829	3.23%	838	718	21	4444	492023	5.01%	7131	5696	73	33762	8.5	2.64	2.5	13.4
24	Rehabilitation	32	15713	0.88%	491	447	16	1167	207860	2.12%	6496	6280	242	14830	13.2	2.94	8.4	19.3
25	Rheumatology	70	12337	0.69%	176	157	6	460	57861	0.59%	827	765	10	2009	4.7	0.99	1.7	8.0
26	Substance Abuse	70	13819	0.77%	197	135	4	1511	62695	0.64%	896	638	19	5440	4.5	1.01	2.9	7.0
27	Surgical Oncology	70	9691	0.54%	138	107	6	538	63676	0.65%	910	773	16	3156	6.6	2.01	2.7	13.1
28	Surgery General	70	146339	8.17%	2091	1895	94	6703	1053701	10.73%	15053	14021	576	44396	7.2	0.98	4.4	9.6
29	Trauma	70	15831	0.88%	226	186	2	841	133920	1.36%	1913	1731	14	9435	8.5	2.08	3.5	13.0
30	Urology	70	47203	2.64%	674	565	86	2658	189328	1.93%	2705	2409	231	8079	4	0.80	2.2	6.2
31	Vascular Surgery	69	19758	1.10%	286	249	36	943	101723	1.04%	1474	1281	363	4779	5.1	1.44	3.2	12.5
32	Ventilator Support	70	20985	1.17%	300	277	3	728	647794	6.60%	9254	8626	31	22758	30.9	6.70	10.3	50.0
33	Spinal Surgery	70	48299	2.70%	690	591	3	2362	203382	2.07%	2905	2523	57	9437	4.2	2.20	1.8	19.0
34	Injuries/complications of prior care	70	15093	0.84%	216	202	32	566	86480	0.88%	1235	1171	144	2782	5.7	1.02	3.4	8.4
35	Gynecology/Oncology	70	10491	0.59%	150	136	2	524	48292	0.49%	690	621	22	2071	4.6	1.42	1.6	11.0

Table 4.2 Adult Antibacterial Drug Consumption at 70 U.S. Academic Medical Centers in 2009 Stratified by Clinical Service Line

	No. of days of therapy (DOTs)						DOTs/1000 patient days (PDs)				DOTs/1000 discharges				DOTs /case	No. of length of therapy (LOT)						LOT/1000 PDs				LOT/1000 discharges				LOT /case	Percent discharges receiving antibiotics	DOTs/LOT ratio		
CSL ID	Sum	% of Total	Mean	Median	Min	Max	Mean*	Median	Min	Max	Mean*	Median	Min	Max	Mean*	Sum	% of Total	Mean	Median	Min	Max	Mean*	Median	Min	Max	Mean*	Median	Min	Max	Mean*	Mean*	Mean*	Min	Max
1	142118	1.75%	2842	2348	2	10720	1269	1238	827	2333	28344	26394	2000	82746	29.5	85177	1.62%	1704	1474	2	7195	760	813	495	2000	16988	17171	2000	33113	17.7	96.1%	1.67	1.00	2.53
2	26771	0.33%	406	70	1	3492	616	655	189	5000	5414	4822	500	17000	9.7	18757	0.36%	284	53	1	2099	432	474	159	2000	3793	3498	500	9000	6.8	56.0%	1.43	1.00	2.57
3	405518	4.98%	5793	4798	83	17028	542	557	324	919	2270	2220	1293	5193	6.0	282243	5.38%	4032	3337	70	11616	377	384	249	572	1580	1529	975	3358	4.2	37.9%	1.44	1.19	1.66
4	389334	4.78%	5562	4365	74	16888	747	753	449	2313	6530	6782	3539	17468	7.0	260458	4.97%	3721	2954	35	13313	500	506	362	1094	4369	4460	2725	10623	4.7	92.6%	1.49	1.24	2.11
5	14109	0.17%	204	168	23	723	1274	1282	775	1841	4266	4179	2000	12409	5.4	9773	0.19%	142	115	18	425	882	882	632	1137	2955	2857	1565	7250	3.7	78.9%	1.44	1.13	1.75
6	12430	0.15%	180	149	24	538	810	801	423	1595	3579	3423	1743	8219	6.1	8543	0.16%	124	103	23	331	557	567	314	889	2460	2411	1371	5125	4.2	59.0%	1.45	1.04	1.97
7	501481	6.16%	7164	6829	284	19417	853	858	598	1150	3951	3826	2437	5745	7.5	319960	6.10%	4571	4434	184	11772	544	548	426	684	2521	2480	1706	3528	4.8	52.6%	1.57	1.31	1.89
8	64167	0.79%	917	824	55	2089	807	836	475	1196	2107	2255	1210	3234	2.6	45278	0.86%	647	568	37	1623	570	593	312	868	1487	1602	761	2153	1.9	80.1%	1.42	1.19	1.81
9	63089	0.78%	1237	705	2	7226	912	916	357	2565	35928	29000	2000	71156	36.3	37606	0.72%	737	437	2	4636	544	536	273	1000	21416	16160	1500	41027	21.6	99.0%	1.68	1.00	3.11
10	125290	1.54%	1816	1106	31	19251	1704	1581	705	2533	14878	13333	6000	32348	16.2	62583	1.19%	907	558	19	9302	851	849	432	1217	7432	7155	3667	15333	8.1	91.8%	2.00	1.40	2.41
11	51514	0.63%	873	607	143	4055	1117	1106	491	1664	8196	7727	2569	17255	8.2	38321	0.73%	650	432	105	2922	831	836	424	1072	6097	5989	2115	12434	6.1	99.6%	1.34	1.09	1.85
12	49809	0.61%	1083	927	63	5737	1221	1230	744	1776	20788	21029	8034	35750	20.9	30154	0.57%	656	558	57	3381	739	761	483	1034	12585	12714	5371	20742	12.6	99.5%	1.65	1.11	1.98
13	23875	0.29%	796	701	89	3037	2039	2138	933	2967	34753	36396	13067	75545	34.9	10721	0.20%	357	286	31	1193	916	927	614	1153	15606	15797	8576	26818	15.7	99.7%	2.23	1.47	3.31
14	363448	4.47%	5192	4463	23	21310	874	791	471	1510	5823	5263	2258	12112	11.7	219748	4.19%	3139	2765	19	9894	528	503	328	704	3521	3356	1467	6692	7.1	49.8%	1.65	1.21	2.16
15	1884609	23.16%	26923	26457	1228	70476	1133	1149	688	1611	4980	5041	2604	7020	8.2	1136175	21.66%	16231	15533	837	47019	683	699	477	897	3002	3074	1733	3784	4.9	60.8%	1.66	1.37	2.04
16	158315	1.95%	2262	2097	55	5265	365	383	217	578	1613	1631	922	2573	6.0	115582	2.20%	1651	1540	41	3724	267	270	176	393	1178	1190	725	1862	4.4	27.0%	1.37	1.21	1.59
17	207850	2.55%	2969	2596	2	7511	772	758	400	1181	5587	5612	2000	12455	6.3	145539	2.77%	2079	1915	2	5313	541	529	342	746	3912	3916	2000	7455	4.4	88.4%	1.43	1.00	1.67
18	276965	3.40%	3957	3605	17	12349	429	441	281	1333	1344	1400	853	3294	2.6	198876	3.79%	2841	2602	12	8547	308	316	190	1000	965	1007	576	2471	1.9	52.0%	1.39	1.16	1.71
19	15387	0.19%	223	156	20	1482	1112	1102	405	1810	3664	3658	1613	7537	5.2	9790	0.19%	142	106	13	914	708	733	305	1019	2332	2406	1082	4173	3.3	69.8%	1.57	1.16	2.03
20	398961	4.90%	5699	5179	1199	20263	825	814	553	1180	3581	3659	2051	6261	3.8	303249	5.78%	4332	3728	942	14752	627	621	451	823	2722	2779	1741	3999	2.9	93.4%	1.32	1.16	1.57
21	92193	1.13%	1317	1136	13	4302	1158	1103	702	1845	5388	5083	1857	8040	6.2	66531	1.27%	950	826	9	2913	835	808	500	1184	3888	3764	1286	6120	4.4	87.5%	1.39	1.09	1.74
22	133909	1.65%	1913	1680	117	8010	1264	1288	841	1857	12424	11778	6627	32149	12.9	86989	1.66%	1243	1118	64	4805	821	842	584	1021	8071	7800	4627	18574	8.4	96.5%	1.54	1.23	1.83
23	47657	0.59%	691	589	4	3159	97	111	29	488	824	820	190	3108	5.8	43186	0.82%	626	523	4	2832	88	101	26	383	747	737	190	2392	5.2	14.3%	1.10	1.00	1.43
24	70943	0.87%	2217	2119	68	4313	341	338	183	535	4515	4433	2878	9504	9.4	58793	1.12%	1837	1752	66	3508	283	282	142	448	3742	3717	2361	7965	7.8	48.0%	1.21	1.03	1.29
25	40240	0.49%	575	509	8	1464	696	672	377	1084	3262	3104	1333	8675	7.0	27051	0.52%	386	358	6	973	468	460	279	673	2193	2122	1000	5310	4.7	46.8%	1.49	1.21	1.74
26	16231	0.20%	232	171	6	838	259	257	101	801	1175	1201	390	4310	6.0	11814	0.23%	169	130	4	592	188	190	91	472	855	893	259	3288	4.4	19.5%	1.37	1.09	1.74
27	58699	0.72%	839	736	13	3211	922	869	290	1365	6057	5726	2167	15860	6.9	39498	0.75%	564	468	12	2245	620	599	230	858	4076	3910	1917	9062	4.6	88.0%	1.49	1.08	1.92
28	1043968	12.83%	14914	14063	655	43720	991	1002	742	1337	7134	7213	4061	11658	7.9	664401	12.67%	9491	8851	417	28019	631	641	458	801	4540	4585	2651	7243	5.0	90.5%	1.57	1.30	1.86
29	87484	1.08%	1250	1195	10	6557	653	679	288	1216	5526	5053	1000	12679	8.7	61698	1.18%	881	856	9	4603	461	481	237	646	3897	3676	824	7864	6.1	63.8%	1.42	1.11	2.02
30	187540	2.30%	2679	2316	368	7754	991	991	544	1593	3973	4295	1615	6298	4.4	134207	2.56%	1917	1693	278	5889	709	716	380	1203	2843	3056	1127	4396	3.2	89.8%	1.40	1.23	1.61
31	76022	0.93%	1102	845	185	3812	747	719	406	1072	3848	3847	1581	7278	5.2	53732	1.02%	779	649	150	2454	528	516	329	668	2720	2754	1282	5722	3.7	74.0%	1.41	1.18	1.66
32	815768	10.02%	11654	10440	55	26554	1259	1281	871	1854	38874	37841	18333	71979	39.4	445265	8.49%	6361	5580	22	16078	687	704	526	887	21218	20880	7333	34615	21.5	98.7%	1.83	1.50	2.50
33	165110	2.03%	2359	2003	36	6704	812	780	459	1578	3419	3284	1750	12000	3.5	129875	2.48%	1855	1599	34	5472	639	632	371	1015	2689	2620	1490	11333	2.8	97.3%	1.27	1.06	1.74
34	98699	1.21%	1410	1316	191	3676	1141	1141	739	1592	6539	6143	4117	11363	8.1	62937	1.20%	899	829	135	2080	728	733	501	972	4170	4086	2587	6801	5.2	80.5%	1.57	1.31	1.99
35	28511	0.35%	407	339	11	1428	590	581	199	933	2718	2594	774	6632	3.3	20890	0.40%	298	257	8	1038	433	439	157	763	1991	1943	608	4000	2.4	82.1%	1.36	1.05	1.76

*** Pooled mean; CSL: Clinical Service Line**





DOTs, days of therapy; LOS, length of stay, LOT, length of therapy; PDs, patient days

Figure 4.1 Antibacterial consumption measured in DOTs/1000 discharges (upper panel) and DOTs/1000 PDs (lower panel), along with the components of each measure, in 5 clinical service lines (CSLs) with different use patterns. The lung transplant, gastroenterology and psychiatry CSLs had very high, average and very low use, respectively, in both measures. The two measures, however, were discrepant in the heart transplant/implant of heart assist system and, to a lesser extent, the ophthalmology CSLs. The extremely long LOS in the former and extremely short one in the latter is responsible for this discrepancy. Measuring LOS and the other components enables identifying their relative contribution to the magnitude of these two measures.

4.2.2 Hospital-wide Aggregated Antibacterial Drug Consumption

The Application of Direct Standardization to the Risk-adjustment of Anti-bacterial Drug Use

Table 4.3 demonstrates the calculations pertaining to the application of direct and indirect standardization to risk-adjust AbC and its components in Hospital #28. The direct standardization procedure entails calculating the expected number of DOTs in the reference population. This is the expected number of DOTs in the reference population had it had the same CSL-specific rates as the study population (e.g., study hospital). For notation, upper case letters will be used throughout this chapter to refer to variables pertaining to the reference population while small case letters will be used for variables pertaining to the study hospitals. Using this notation, the expected number of DOTs in the reference population is given by

$$E(D_i) = \sum_{j=1}^{k} \frac{d_{ij}}{n_{ij}} N_j \qquad (4.5)$$

Where $E(D_i)$is the expected number of DOTs of the reference population using the CSL-specific rates of the i^{th} study population (i= 1, 2,..., m where m is the number of study populations), k is the number of CSLs (i.e., strata), d_{ij} is the number of DOTs in the j^{th} CSL of the i^{th} study population (j= 1, 2,..., k), n_{ij} is the number of discharges in the j^{th} CSL of the i^{th} study

population and N_j is the number of discharges in the j^{th} CSL of the reference population.

Applying Equation 4.5 to Hospital #28

$$E(D_{28}) = \left(\frac{5081}{123}\right)5014 + \left(\frac{31}{4}\right)4945 + \ldots + \left(\frac{246}{95}\right)10491 = 11240519 \text{ DOTs}$$

The expected number of DOTs (Equation 4.5) can be transformed to DSR by dividing it by the total number of discharges in the reference population.

$$(\text{DSR}_i)_{D/D} = \frac{\textit{Expected total number of DOTs in reference population}}{\textit{Total number of discharges in reference population}} = \frac{\sum_{j=1}^{k} \frac{d_{ij}}{n_{ij}} N_j}{N} \qquad (4.6)$$

Where $(\text{DSR}_i)_{D/D}$ is the directly standardized rate for the DOTs/1000 discharges measure, N is the total number of discharges of the reference population ($N = \Sigma N_j$) and the other notation is as defined before. Applying Equation 4.6 to Hospital #28 and multiplying by 1000 to express the rate in DOTs/1000 discharges

$$(DSR_{28})_{D/D} = \frac{11240519}{1791172} = 6.2755 \text{ DOTs/discharge} = 6276 \text{ DOTs/1000 discharges}$$

$(\text{DSR}_{28})_{D/D}$ represents the expected AbC rate of the reference population (in DOTs/1000 discharges) had it had the same CSL-specific rates as Hospital #28 or, alternatively, the expected AbC rate of Hospital #28 had it had the same CSL distribution as the reference population. It is worth mentioning that Equation 4.6 can be simplified by expressing DSR as a weighted

average of the CSL-specific rates of the study population where the corresponding weights are supplied by the reference population (Table 4.3).

$$(DSR_i)_{D/D} = \sum_{j=1}^{k} (r_{ij})_{d/d} W_j \qquad (4.7)$$

Where $(r_{ij})_{d/d}$ is the DOTs/1000 discharges rate in the j^{th} CSL of the i^{th} study population ($(r_{ij})_{d/d} = d_{ij}/n_{ij}$) and W_j is the weight of the j^{th} CSL of the reference population ($W_j = N_j/N$). Equation 4.7 shows that if two populations have the same CSL-specific rates then their DSRs will necessarily be identical as long as they are standardized to the same reference population.

The expected number of DOTs can also be used to obtain a relative risk type measure; the expected-to-observed ratio, which is calculated as follows

$$(E/O_i)_D = \frac{Expected\ total\ number\ of\ DOTs\ in\ reference\ population}{Observed\ total\ number\ of\ DOTs\ in\ reference\ population} = \frac{\sum_{j=1}^{k} \frac{d_{ij}}{n_{ij}} N_j}{D} \qquad (4.8)$$

Where $(E/O_i)_D$ is the i^{th} expected-to-observed ratio for DOTs, D is the (observed) total number of DOTs of the reference population ($D = \Sigma D_j$ where D_j is the number of DOTs in the j^{th} CSL of the reference population) and the other notation is as defined before. It should be obvious that, by dividing both the numerator and denominator in Equation 4.8 by the total number of discharges of the reference population (N), the E/O ratio can be

equivalently expressed as the ratio of DSR to the crude rate in the reference population ($R_{D/D}$).

$$(E/O_i)_{D/D} = \frac{(DSR_i)_{D/D}}{R_{D/D}} \tag{4.9}$$

Applying Equation 4.8 and Equation 4.9 to Hospital #28

$$(E/O_{28})_D = \frac{11240519}{8138014} = (E/O_{28})_{D/D} = \frac{6276}{4543} = 1.38$$

Accordingly, one can interpret $(E/O_{28})_{D/D}$ as an expected 38% increase in the AbC rate of the reference population had it had the same CSL-specific rates as Hospital #28. In other words, the (adjusted) AbC rate of Hospital #28 was 38% higher than the crude rate of the reference population.

While the E/O ratio provides a useful comparison between DSR and the crude rate in the reference population, its greatest asset lies in its ability to facilitate the comparison of DSRs across different study populations. It should be evident that for any two populations, the ratio of their E/O ratios equals the ratio of their DSRs.

$$\frac{(E/O)_{population\ A}}{(E/O)_{population\ B}} = \frac{DSR_{population\ A}}{DSR_{population\ B}} \tag{4.10}$$

Applying Equation 4.10 to compare DSR_{28} with DSR_{59} which was the lowest among the 70 hospitals (the referent hospital)

$$\frac{(DSR_{28})_{D/D}}{(DSR_{59})_{D/D}} = \frac{6276}{3396} = 1.85$$

Therefore, the adjusted (i.e., standardized) AbC rate of Hospital #28 was about 85% higher than that of Hospital #59. However, it should be noted that all study populations should be standardized to the same reference population for Equation 4.10 to hold and the DSRs to be directly comparable. This was not possible in this study since the CSL composition varied from one hospital to another. However, the CSLs that were not common to all hospitals had such small weights (Table 4.1) that the differences between the different reference populations were generally marginal. The ratio of the observed rates of the two hospitals was 2.21.

The Application of Indirect Standardization to the Risk-adjustment of Anti-bacterial Drug consumption

An example of the application of indirect standardization to the risk-adjustment of AbC is presented in Table 4.4 using Hospital #28 as a representative of the study population. The indirect standardization procedure is a mirror image of its direct counterpart. That is, the reference population is the source of the CSL-specific AbC rates while the study population provides the corresponding number of discharges. Then, the expected number of DOTs in the study population is calculated as follows

$$e(d_i) = \sum_{j=1}^{k} \frac{D_j}{N_j} n_{ij} \qquad (4.11)$$

Where $e(d_i)$ is the expected number of DOTs in the i^{th} study population and the other notation is as defined before. Equation 4.11 represents the expected number of DOTs in the study population had it had the same CSL-specific rates as the reference population.

Applying Equation 4.11 to Hospital #28

$$e(d_{28}) = \left(\frac{142118}{5014}\right)123 + \left(\frac{26771}{4945}\right)4 + \ldots + \left(\frac{28511}{10491}\right)95 = 104712 \text{ DOTs}$$

The statistic that is usually reported in indirect standardization is the observed-to-expected ratio which is given by

$$(o/e_i)_d = \frac{\textit{Observed total number of DOTs in study population}}{\textit{Expected total number of DOTs in study population}} = \frac{d_i}{\sum_{j=1}^{k} \frac{D_j}{N_j} n_{ij}} \qquad (4.12)$$

Where $(o/e_i)_d$ is the observed-to-expected ratio (for DOTs) of the i^{th} study population, d_i is the (observed) total number of DOTs in the i^{th} study population ($d_i = \Sigma d_{ij}$) and the other notation is as defined before.

Applying Equation 4.8 to Hospital #28

$$(o/e_{28})_d = \frac{145654}{104712} = 1.39$$

Thus, the *o/e* ratio obtained through indirect standardization was virtually identical to the E/O ratio obtained through the direct standardization procedure for Hospital #28, as well as for almost all the other hospitals with

the notable exception of Hospital #61 (Figure 4.2). For both ratios, a value above 1 indicates higher than expected use while a value below 1 indicates lower than expected use.

In analogy to Equation 4.9 which can be rearranged to express DSR as the product of the E/O ratio and the crude rate in the reference population, ISR can similarly be expressed as the product of the *o/e* ratio and the latter

$$(ISR_i)_{d/d} = \left(o / e_i\right)_{d/d} \times R_{D/D} \qquad (4.13)$$

Where $(ISR_i)_{d/d}$ is the indirectly standardized rate of the i^{th} study population and the rest of the notation is as defined before.

Applying Equation 4.8 to Hospital #28

$$(ISR_{28})_{d/d} = 1.391 \times 4543 = 6319 \text{ DOTs/1000 discharges}$$

Obviously, comparing the E/O ratio to the *o/e* ratio is equivalent to comparing DSR to ISR. However, it should be noted that two populations that have identical CSL-specific rates may have quite different ISRs in spite of having identical DSRs.

Table 4.3 An Example of the Application of Direct Standardization to the Risk-adjustment of Antibacterial Consumption in Hospital #28

Reference Population, Observed												
CSL ID (j)	No. of discharges (N_j)	No. of cases (N_j')	No. of patient days (PD_j)	Observed no. of DOTs (D_j)	Observed no. of LOT (L_j)	LOT/case $((R_j)_{L/C} = L_j/N_j')$	Percent no. of cases ($P_j = N_j'/N_j$)	DOTs/LOT ratio ($DL_j = D_j/L_j$)	Mean LOS ($LOS_j = PD_j/N_j$)	Weights ($W_j = N_j/N_i$)	DOT/ discharge $((R_j)_{D/D} = D_j/N_j)$	LOT/ discharge $((R_j)_{L/D} = L_j/N_j)$
1	5014	4818	112030	142118	85177	17.7	96.1%	1.67	22.3	0.0028	28.344	16.988
2	4945	2770	43445	26771	18757	6.8	56.0%	1.43	8.8	0.0028	5.414	3.793
3	178678	67757	748276	405518	282243	4.2	37.9%	1.44	4.2	0.0998	2.270	1.580
4	59619	55233	521190	389334	260458	4.7	92.6%	1.49	8.7	0.0333	6.530	4.369
5	3307	2610	11079	14109	9773	3.7	78.9%	1.44	3.4	0.0018	4.266	2.955
6	3473	2048	15351	12430	8543	4.2	59.0%	1.45	4.4	0.0019	3.579	2.460
7	126928	66721	588163	501481	319960	4.8	52.6%	1.57	4.6	0.0709	3.951	2.521
8	30453	24388	79471	64167	45278	1.9	80.1%	1.42	2.6	0.0170	2.107	1.487
9	1756	1739	69171	63089	37606	21.6	99.0%	1.68	39.4	0.0010	35.928	21.416
10	8421	7728	73535	125290	62583	8.1	91.8%	2.00	8.7	0.0047	14.878	7.432
11	6285	6263	46100	51514	38321	6.1	99.6%	1.34	7.3	0.0035	8.196	6.097
12	2396	2385	40782	49809	30154	12.6	99.5%	1.65	17.0	0.0013	20.788	12.585
13	687	685	11710	23875	10721	15.7	99.7%	2.23	17.0	0.0004	34.753	15.606
14	62416	31088	415843	363448	219748	7.1	49.8%	1.65	6.7	0.0348	5.823	3.521
15	378417	229996	1663899	1884609	1136175	4.9	60.8%	1.66	4.4	0.2113	4.980	3.002
16	98160	26455	433657	158315	115582	4.4	27.0%	1.37	4.4	0.0548	1.613	1.177
17	37203	32900	269137	207850	145539	4.4	88.4%	1.43	7.2	0.0208	5.587	3.912
18	206121	107161	646232	276965	198876	1.9	52.0%	1.39	3.1	0.1151	1.344	0.965
19	4199	2932	13838	15387	9790	3.3	69.8%	1.57	3.3	0.0023	3.664	2.332
20	111418	104023	483740	398961	303249	2.9	93.4%	1.32	4.3	0.0622	3.581	2.722
21	17110	14979	79645	92193	66531	4.4	87.5%	1.39	4.7	0.0096	5.388	3.888
22	10778	10406	105930	133909	86989	8.4	96.5%	1.54	9.8	0.0060	12.424	8.071
23	57829	8280	492023	47657	43186	5.2	14.3%	1.10	8.5	0.0323	0.824	0.747
24	15713	7550	207860	70943	58793	7.8	48.0%	1.21	13.2	0.0088	4.515	3.742
25	12337	5768	57861	40240	27051	4.7	46.8%	1.49	4.7	0.0069	3.262	2.193
26	13819	2697	62695	16231	11814	4.4	19.5%	1.37	4.5	0.0077	1.175	0.855
27	9691	8528	63676	58699	39498	4.6	88.0%	1.49	6.6	0.0054	6.057	4.076
28	146339	132451	1053701	1043968	664401	5.0	90.5%	1.57	7.2	0.0817	7.134	4.540
29	15831	10097	133920	87484	61698	6.1	63.8%	1.42	8.5	0.0088	5.526	3.897
30	47203	42367	189328	187540	134207	3.2	89.8%	1.40	4.0	0.0264	3.973	2.843
31	19758	14626	101723	76022	53732	3.7	74.0%	1.41	5.1	0.0110	3.848	2.720
32	20985	20712	647794	815768	445265	21.5	98.7%	1.83	30.9	0.0117	38.874	21.218
33	48299	46996	203382	165110	129875	2.8	97.3%	1.27	4.2	0.0270	3.418	2.689
34	15093	12151	86480	98699	62937	5.2	80.5%	1.57	5.7	0.0084	6.539	4.170
35	10491	8608	48292	28511	20890	2.4	82.1%	1.36	4.6	0.0059	2.718	1.991
Total	$N_i = \sum N_j$ = 1791172	$N_i' = \sum N_j'$ = 1125916	$PD_i = \sum PD_j$ = 9820959	$D_i = \sum D_j$ = 8138014	$L_i = \sum L_j$ = 5245400	$(R_i)_{L/C} = L_i/N_i'$ = 4.7	$P_i = N_i'/N_i$ = 62.9 %	$DL_i = D_i/L_i$ = 1.55	$LOS_i = PD_i/N_i$ = 5.5	$W_i = \sum W_j$ = 1.00	$(R_i)_{D/D} = D_i/N_i$ = 4.543	$(R_i)_{L/D} = L_i/D_i$ = 2.928

Reference Population, Expected (Direct Standardization)										
CSL ID (j)	Expected no. of cases $(E(N'_{ij}) = p_{ij} \times N_j)$	Expected no. of patient days $(E(PD_{ij}) = los_{ij} \times N_j)$	Expected no. of DOTs $(E(D_{ij}) = (r_{ij})_{d/d} \times N_j)$	Expected no. of LOT $(E(L_{ij}) = (r_{ij})_{l/d} \times N_j)$	Expected LOT/case $(E(R_{ij})_{L/C} = E(L_{ij})/(E(N'_{ij}))$	Expected perecent of cases $(E(P_{ij}) = E(N'_{ij})/N_j)$	Expected DOTs/LOT ratio $(E(DL_{ij}) = E(D_{ij})/E(L_{ij}))$	Expected mean LOS $(E(LOS_{ij}) = E(PD_{ij})/N_j)$	Expected DOTs/ discharge $(E(R_{ij})_{D/D} = E(D_{ij})/N_j)$	$(r_{ij})_{d/d} * W_j$
1	4973	132035	207123	118787	23.9	99.2%	1.74	26.3	41.309	0.11564
2	4945	59340	38324	30906	6.3	100.0%	1.24	12.0	7.750	0.02140
3	91968	966402	735258	470482	5.1	51.5%	1.56	5.4	4.115	0.41049
4	57542	538159	556301	323690	5.6	96.5%	1.72	9.0	9.331	0.31058
5	2606	10222	15232	9721	3.7	78.8%	1.57	3.1	4.606	0.00850
6	1858	12519	7996	7188	3.9	53.5%	1.11	3.6	2.302	0.00446
7	78722	738260	712426	446775	5.7	62.0%	1.59	5.8	5.613	0.39774
8	27494	82194	88184	60329	2.2	90.3%	1.46	2.7	2.896	0.04923
9	1756	89821	99234	54252	30.9	100.0%	1.83	51.2	56.512	0.05540
10	7966	91038	143385	68278	8.6	94.6%	2.10	10.8	17.027	0.08005
11	6285	45397	56089	42317	6.7	100.0%	1.33	7.2	8.924	0.03131
12	2396	68778	84330	49699	20.7	100.0%	1.70	28.7	35.196	0.04708
13	687	11133	25997	10820	15.8	100.0%	2.40	16.2	37.841	0.01451
14	42711	599213	713853	417692	9.8	68.4%	1.71	9.6	11.437	0.39854
15	258526	1737018	2386133	1344847	5.2	68.3%	1.77	4.6	6.306	1.33216
16	30593	442658	200731	145457	4.8	31.2%	1.38	4.5	2.045	0.11207
17	32872	295163	285469	185966	5.7	88.4%	1.54	7.9	7.673	0.15938
18	123510	606265	296135	211990	1.7	59.9%	1.40	2.9	1.437	0.16533
19	3643	13406	19730	11788	3.2	86.7%	1.67	3.2	4.699	0.01102
20	100441	510071	474396	352732	3.5	90.1%	1.34	4.6	4.258	0.26485
21	16726	77572	128581	80103	4.8	97.8%	1.61	4.5	7.515	0.07179
22	10778	64824	95830	62559	5.8	100.0%	1.53	6.0	8.891	0.05350
23	8897	144016	28358	22242	2.5	15.4%	1.28	2.5	0.490	0.01583
24	10153	256968	105076	85495	8.4	64.6%	1.23	16.4	6.687	0.05866
25	7368	66483	69139	40781	5.5	59.7%	1.70	5.4	5.604	0.03860
26	3418	81725	14711	10699	3.1	24.7%	1.38	5.9	1.065	0.00821
27	9601	53704	59447	42847	4.5	99.1%	1.39	5.5	6.134	0.03319
28	142588	1048041	1104300	724388	5.1	97.4%	1.52	7.2	7.546	0.61652
29	11534	192686	200714	124500	10.8	72.9%	1.61	12.2	12.679	0.11206
30	46409	204074	243958	172132	3.7	98.3%	1.42	4.3	5.168	0.13620
31	14700	100371	86856	59274	4.0	74.4%	1.47	5.1	4.396	0.04849
32	20921	905756	1510471	726389	34.7	99.7%	2.08	43.2	71.979	0.84329
33	46634	264257	271474	187922	4.0	96.6%	1.44	5.5	5.621	0.15156
34	12879	114640	148113	88814	6.9	85.3%	1.67	7.6	9.813	0.08269
35	9939	52565	27166	22418	2.3	94.7%	1.21	5.0	2.589	0.01517
Total	$E(N'_i) = \sum E(N'_{ij}) =$ **1254037**	$E(PD_i) = \sum E(PD_{ij}) =$ **10676776**	$E(D_i) = \sum E(D_{ij}) =$ **11240519**	$E(L_i) = \sum E(L_{ij}) =$ **6814277**	$E(R_i)_{L/C} = E(L_i)/(E(N'_i) =$ **5.4**	$(E(P_i) = E(N'_i)/N_i) =$ **70.0%**	$(E(DL_i) = E(D_i)/E(L_i)$ **= 1.65**	$(E(LOS_i) = E(PD_i)/N_i)$ **= 6.0**	$E(R_i)_{D/D} = E(D_i)/N_i$ **= 6.276**	$E(R_i)_{D/D} = [\sum (r_{ij})_{d/d} W_j]$ **= 6.276**

Reference Population, E/O ratios					
CSL ID (j)	E/O ratio for LOT/case $((E/O_{ij})_{L/C} = E(R_{ij})_{L/C}/(R_{ij})_{L/C})$	E/O ratio for percent no. of cases $((E/O_{ij})_{p} = E(P_{ij})/P_{ij})$	E/O ratio for DOTs/LOT ratio $((E/O_{ij})_{DL} = E(DL_{ij})/DL_{ij})$	E/O ratio for mean LOS $((E/O_{ij})_{LOS} = E(LOS_{ij})/LOS_{ij})$	E/O ratio for DOTs/discharge $((E/O_{ij})_{D/D} = E(R_{ij})_{D/D}/(R_{ij})_{D/D})$
1	1.35	1.03	1.05	1.18	1.46
2	0.92	1.79	0.87	1.37	1.43
3	1.23	1.36	1.09	1.29	1.81
4	1.19	1.04	1.15	1.03	1.43
5	1.00	1.00	1.09	0.92	1.08
6	0.93	0.91	0.76	0.82	0.64
7	1.18	1.18	1.02	1.26	1.42
8	1.18	1.13	1.03	1.03	1.37
9	1.43	1.01	1.09	1.30	1.57
10	1.06	1.03	1.05	1.24	1.14
11	1.10	1.00	0.99	0.98	1.09
12	1.64	1.00	1.03	1.69	1.69
13	1.01	1.00	1.08	0.95	1.09
14	1.38	1.37	1.03	1.44	1.96
15	1.05	1.12	1.07	1.04	1.27
16	1.09	1.16	1.01	1.02	1.27
17	1.28	1.00	1.07	1.10	1.37
18	0.92	1.15	1.00	0.94	1.07
19	0.97	1.24	1.06	0.97	1.28
20	1.20	0.97	1.02	1.05	1.19
21	1.08	1.12	1.16	0.97	1.39
22	0.69	1.04	1.00	0.61	0.72
23	0.48	1.07	1.16	0.29	0.60
24	1.08	1.34	1.02	1.24	1.48
25	1.18	1.28	1.14	1.15	1.72
26	0.71	1.27	1.00	1.30	0.91
27	0.96	1.13	0.93	0.84	1.01
28	1.01	1.08	0.97	0.99	1.06
29	1.77	1.14	1.14	1.44	2.29
30	1.17	1.10	1.01	1.08	1.30
31	1.10	1.01	1.04	0.99	1.14
32	1.62	1.01	1.13	1.40	1.85
33	1.46	0.99	1.14	1.30	1.64
34	1.33	1.06	1.06	1.33	1.50
35	0.93	1.15	0.89	1.09	0.95
Total	$(E/O_i)_{L/C} = E(R_i)_{L/C}/(R_i)_{L/C} = 1.15$	$(E/O_i)_{p} = E(P_i)/P_i = 1.11$	$(E/O_i)_{DL} = E(DL_i)/DL_i = 1.06$	$(E/O_i)_{LOS} = E(LOS_i)/LOS_i = 1.09$	$(E/O_i)_{D/D} = E(R_i)_{D/D}/(R_i)_{D/D} = 1.38$

Table 4.4 An Example of the Application of Indirect Standardization to the Risk-adjustment of Antibacterial Consumption in Hospital #28

Hospital 28 (Study Population), Observed											
CSL ID (j)	No. of discharges (n_{ij})	No. of cases (n'_{ij})	No. of patient days (pd_{ij})	No. of DOTs (d_{ij})	No. of LOT (l_{ij})	LOT/case ($(r_{ij})_{l/c} = l_{ij}/n'_{ij}$)	Percent no. of cases ($p_{ij} = n'_{ij}/n_{ij}$)	DOTs/LOT ratio ($dl_{ij} = d_{ij}/l_{ij}$)	Mean LOS $los_{ij} = pd_{ij}/n_{ij}$)	DOT/ discharge ($(r_{ij})_{d/d} = d_{ij}/n_{ij}$)	LOT/ discharge ($(r_{ij})_{l/d} = l_{ij}/n_{ij}$)
1	123	122	3239	5081	2914	23.9	99.2%	1.74	26.3	41.309	23.691
2	4	4	48	31	25	6.3	100.0%	1.24	12.0	7.750	6.250
3	1461	752	7902	6012	3847	5.1	51.5%	1.56	5.4	4.115	2.633
4	976	942	8810	9107	5299	5.6	96.5%	1.72	9.0	9.331	5.429
5	33	26	102	152	97	3.7	78.8%	1.57	3.1	4.606	2.939
6	43	23	155	99	89	3.9	53.5%	1.11	3.6	2.302	2.070
7	1356	841	7887	7611	4773	5.7	62.0%	1.59	5.8	5.613	3.520
8	422	381	1139	1222	836	2.2	90.3%	1.46	2.7	2.896	1.981
9	86	86	4399	4860	2657	30.9	100.0%	1.83	51.2	56.512	30.895
10	37	35	400	630	300	8.6	94.6%	2.10	10.8	17.027	8.108
11	251	251	1813	2240	1690	6.7	100.0%	1.33	7.2	8.924	6.733
12	163	163	4679	5737	3381	20.7	100.0%	1.70	28.7	35.196	20.742
13	44	44	713	1665	693	15.8	100.0%	2.40	16.2	37.841	15.750
14	643	440	6173	7354	4303	9.8	68.4%	1.71	9.6	11.437	6.692
15	3109	2124	14271	19604	11049	5.2	68.3%	1.77	4.6	6.306	3.554
16	1046	326	4717	2139	1550	4.8	31.2%	1.38	4.5	2.045	1.482
17	756	668	5998	5801	3779	5.7	88.4%	1.54	7.9	7.673	4.999
18	2283	1368	6715	3280	2348	1.7	59.9%	1.40	2.9	1.437	1.028
19	83	72	265	390	233	3.2	86.7%	1.67	3.2	4.699	2.807
20	609	549	2788	2593	1928	3.5	90.1%	1.34	4.6	4.258	3.166
21	534	522	2421	4013	2500	4.8	97.8%	1.61	4.5	7.515	4.682
22	138	138	830	1227	801	5.8	100.0%	1.53	6.0	8.891	5.804
23	104	16	259	51	40	2.5	15.4%	1.28	2.5	0.490	0.385
24	195	126	3189	1304	1061	8.4	64.6%	1.23	16.4	6.687	5.441
25	144	86	776	807	476	5.5	59.7%	1.70	5.4	5.604	3.306
26	93	23	550	99	72	3.1	24.7%	1.38	5.9	1.065	0.774
27	216	214	1197	1325	955	4.5	99.1%	1.39	5.5	6.134	4.421
28	2263	2205	16207	17077	11202	5.1	97.4%	1.52	7.2	7.546	4.950
29	140	102	1704	1775	1101	10.8	72.9%	1.61	12.2	12.679	7.864
30	832	818	3597	4300	3034	3.7	98.3%	1.42	4.3	5.168	3.647
31	250	186	1270	1099	750	4.0	74.4%	1.47	5.1	4.396	3.000
32	327	326	14114	23537	11319	34.7	99.7%	2.08	43.2	71.979	34.615
33	174	168	952	978	677	4.0	96.6%	1.44	5.5	5.621	3.891
34	225	192	1709	2208	1324	6.9	85.3%	1.67	7.6	9.813	5.884
35	95	90	476	246	203	2.3	94.7%	1.21	5.0	2.589	2.137
Total	$n_i = \sum n_{ij}$ = 19258	$n'_i = \sum n'_{ij}$ = 14229	$pd_i = \sum pd_{ij}$ = 131464	$d_i = \sum d_{ij}$ = 145654	$l_i = \sum l_{ij}$ = 87306	$(r_i)_{l/c} = l_i/n'_i$ = 6.1	$p_i = n'_i/n_i$ = 74.9 %	$dl_i = d_i/l_i$ = 1.67	$los_i = pd_i/n_i$ = 6.8	$(r_i)_{d/d} = d_i/n_i$ = 7.563	$(r_i)_{l/d} = l_i/n_i$ = 4.533

Hospital 28, Expected (Indirect Standardization)									
CSL ID (j)	Expected no. of cases $(e(n'_{ij}) = P_j \times n_{ij})$	Expected no. of patient days $(e(pd_{ij}) = LOS_j \times n_{ij})$	Expected no. of DOTs $(e(d_{ij}) = (R_j)_{D/D} \times n_{ij})$	Expected no. of LOT $(e(l_{ij}) = (R_j)_{L/D} \times n_{ij})$	Expected LOT/case $((r_{ij})_{l/c} = e(l_{ij})/(e(n'_{ij}))$	Expected perecent of cases $(e(p_{ij}) = e(n'_{ij})/n_{ij})$	Expected DOTs/LOT ratio $(e(dl_{ij}) = e(d_{ij})/e(l_{ij}))$	Expected mean LOS $(e(los_{ij}) = e(pd_{ij})/n_{ij})$	Expected DOTs/ discharge $((r_{ij})_{d/d} = e(d_{ij})/n_{ij})$
1	118	2748	3486	2090	17.7	96.1%	1.67	22.3	28.344
2	2	35	22	15	6.8	56.0%	1.43	8.8	5.414
3	554	6118	3316	2308	4.2	37.9%	1.44	4.2	2.270
4	904	8532	6374	4264	4.7	92.6%	1.49	8.7	6.530
5	26	111	141	98	3.7	78.9%	1.44	3.4	4.266
6	25	190	154	106	4.2	59.0%	1.45	4.4	3.579
7	713	6283	5357	3418	4.8	52.6%	1.57	4.6	3.951
8	338	1101	889	627	1.9	80.1%	1.42	2.6	2.107
9	85	3388	3090	1842	21.6	99.0%	1.68	39.4	35.928
10	34	323	550	275	8.1	91.8%	2.00	8.7	14.878
11	250	1841	2057	1530	6.1	99.6%	1.34	7.3	8.196
12	162	2774	3389	2051	12.6	99.5%	1.65	17.0	20.788
13	44	750	1529	687	15.7	99.7%	2.23	17.0	34.753
14	320	4284	3744	2264	7.1	49.8%	1.65	6.7	5.823
15	1890	13670	15484	9335	4.9	60.8%	1.66	4.4	4.980
16	282	4621	1687	1232	4.4	27.0%	1.37	4.4	1.613
17	669	5469	4224	2957	4.4	88.4%	1.43	7.2	5.587
18	1187	7158	3068	2203	1.9	52.0%	1.39	3.1	1.344
19	58	274	304	194	3.3	69.8%	1.57	3.3	3.664
20	569	2644	2181	1658	2.9	93.4%	1.32	4.3	3.581
21	467	2486	2877	2076	4.4	87.5%	1.39	4.7	5.388
22	133	1356	1715	1114	8.4	96.5%	1.54	9.8	12.424
23	15	885	86	78	5.2	14.3%	1.10	8.5	0.824
24	94	2580	880	730	7.8	48.0%	1.21	13.2	4.515
25	67	675	470	316	4.7	46.8%	1.49	4.7	3.262
26	18	422	109	80	4.4	19.5%	1.37	4.5	1.175
27	190	1419	1308	880	4.6	88.0%	1.49	6.6	6.057
28	2048	16295	16144	10274	5.0	90.5%	1.57	7.2	7.134
29	89	1184	774	546	6.1	63.8%	1.42	8.5	5.526
30	747	3337	3306	2366	3.2	89.8%	1.40	4.0	3.973
31	185	1287	962	680	3.7	74.0%	1.41	5.1	3.848
32	323	10094	12712	6938	21.5	98.7%	1.83	30.9	38.874
33	169	733	595	468	2.8	97.3%	1.27	4.2	3.418
34	181	1289	1471	938	5.2	80.5%	1.57	5.7	6.539
35	78	437	258	189	2.4	82.1%	1.36	4.6	2.718
Total	$e(n'_i) = \sum e(n'_{ij}) =$ **13035**	$e(pd_i) = \sum e(pd_{ij}) =$ **116795**	$e(d_i) = \sum e(d_{ij}) =$ **104711**	$e(l_i) = \sum e(l_{ij}) =$ **66824**	$e(r_i)_{l/c} = e(l_i)/(e(n'_i) =$ **5.1**	$(e(p_i) = e(n'_i)/n_i) =$ **67.7%**	$(e(dl_i) = e(d_i)/e(l_i)) =$ **1.57**	$(e(los_i) = e(pd_i)/n_i) =$ **6.1**	$e(r_i)_{d/d} = e(d_i)/n_i =$ **5.437**

Hospital 28, o/e ratios						
CSL ID (j)	o/e ratio for LOT/case $((o/e_{ij})_{l/c} = (r_{ij})_{l/c}/e(r_{ij})_{l/c})$	o/e ratio for percent no. of cases $((o/e_{ij})_{p} = p_{ij}/e(p_{ij}))$	o/e ratio for DOTs/LOT ratio $((o/e_{ij})_{dl} = dl_{ij}/e(dl_{ij}))$	o/e ratio for mean LOS $((o/e_{ij})_{los} = los_{ij}/e(los_{ij}))$	o/e ratio for DOT/ discharge $((o/e_{ij})_{d/d} = (r_{ij})_{d/d}/e(r_{ij})_{d/d})$	Indirectly Standardized Rate $((ISR_{ij})_{d/d} = (o/e_{ij})_{d/d} \times (R_j)_{D/D})$
1	1.35	1.03	1.05	1.18	1.46	41.309
2	0.92	1.79	0.87	1.37	1.43	7.750
3	1.23	1.36	1.09	1.29	1.81	4.115
4	1.19	1.04	1.15	1.03	1.43	9.331
5	1.00	1.00	1.09	0.92	1.08	4.606
6	0.93	0.91	0.76	0.82	0.64	2.302
7	1.18	1.18	1.02	1.26	1.42	5.613
8	1.18	1.13	1.03	1.03	1.37	2.896
9	1.43	1.01	1.09	1.30	1.57	56.512
10	1.06	1.03	1.05	1.24	1.14	17.027
11	1.10	1.00	0.99	0.98	1.09	8.924
12	1.64	1.00	1.03	1.69	1.69	35.196
13	1.01	1.00	1.08	0.95	1.09	37.841
14	1.38	1.37	1.03	1.44	1.96	11.437
15	1.05	1.12	1.07	1.04	1.27	6.306
16	1.09	1.16	1.01	1.02	1.27	2.045
17	1.28	1.00	1.07	1.10	1.37	7.673
18	0.92	1.15	1.00	0.94	1.07	1.437
19	0.97	1.24	1.06	0.97	1.28	4.699
20	1.20	0.97	1.02	1.05	1.19	4.258
21	1.08	1.12	1.16	0.97	1.39	7.515
22	0.69	1.04	1.00	0.61	0.72	8.891
23	0.48	1.07	1.16	0.29	0.60	0.490
24	1.08	1.34	1.02	1.24	1.48	6.687
25	1.18	1.28	1.14	1.15	1.72	5.604
26	0.71	1.27	1.00	1.30	0.91	1.065
27	0.96	1.13	0.93	0.84	1.01	6.134
28	1.01	1.08	0.97	0.99	1.06	7.546
29	1.77	1.14	1.14	1.44	2.29	12.679
30	1.17	1.10	1.01	1.08	1.30	5.168
31	1.10	1.01	1.04	0.99	1.14	4.396
32	1.62	1.01	1.13	1.40	1.85	71.979
33	1.46	0.99	1.14	1.30	1.64	5.621
34	1.33	1.06	1.06	1.33	1.50	9.813
35	0.93	1.15	0.89	1.09	0.95	2.589
Total	$(o/e_i)_{l/c} = (r_i)_{l/c}/e(r_i)_{l/c} = 1.20$	$(o/e_i)_{p} = p_i/e(p_i) = 1.11$	$(o/e_i)_{dl} = dl_i/e(dl_i) = 1.06$	$(o/e_{los})_i = los_i/e(los_i) = 1.13$	$(o/e_i)_{d/d} = (r_i)_{d/d}/e(r_i)_{d/d} = 1.39$	$(ISR_i)_{d/d} = (o/e_i)_{d/d} \times (R_i)_{D/D} = 6.319$

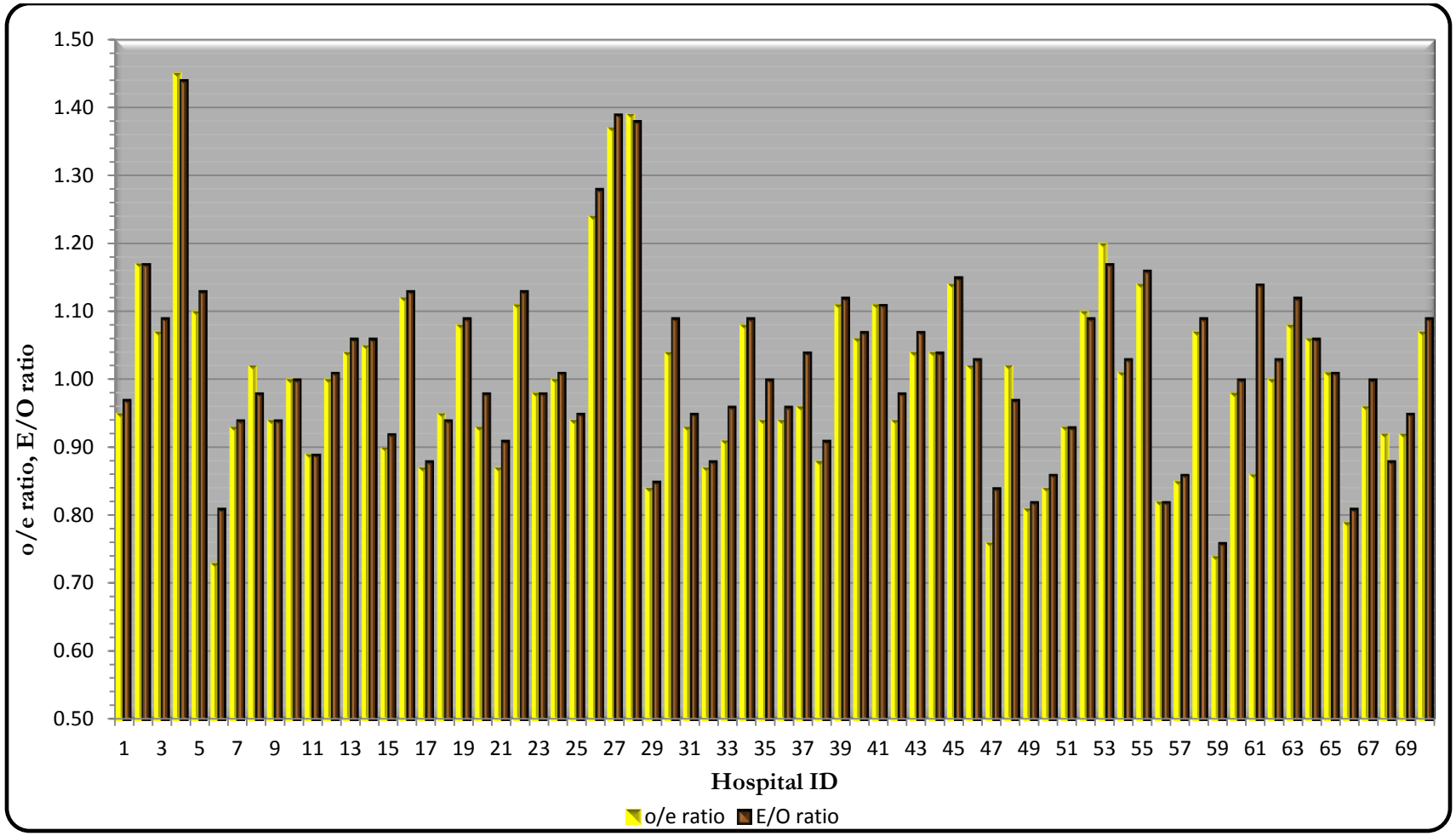


Figure 4.2 Observed-to-expected (o/e) and Expected-to-observed (E/O) ratios derived from the application of indirect and direct standardization, respectively, to the risk-adjustment of antibacterial drug consumption rates (measured in days of therapy per one thousand discharges) at 70 US academic medical centers in 2009. The two ratios are interpreted similarly with a value >1 indicating higher than expected use and a value < 1 indicating lower than expected use. The O/E ratio ranged from 0.76 (Hospital #59) to 1.44 (Hospital #4) while the o/e ratio ranged from 0.73 (Hospital #6) to 1.45 (Hospital #4). The two ratios were in agreement with a few exceptions of which Hospital #61 was the most notable.

Risk-adjusted Components of Antibacterial Drug Consumption

As shown in Table 4.3, direct standardization can also be used to derive hospital-wide expected values of the components of AbC. Using direct standardization, the expected LOT/case is given by

$$E(R_i)_{L/C} = \frac{Expected\ \ total\ number\ of\ \ LOT\ \ in\ reference\ population}{Expected\ total\ number\ of\ \ cases\ in\ reference\ population} = \frac{\sum_{j=1}^{k} \frac{l_{ij}}{n_{ij}} N_j}{\sum_{j=1}^{k} p_{ij} N_j} \quad (4.14)$$

where $E(R_i)_{L/C}$ is the expected LOT/case rate in the reference population, l_{ij} is the number of LOT in the j^{th} CSL of the i^{th} study population, p_{ij} is the proportion of cases in the j^{th} CSL of the i^{th} study population and the other notation is as defined before.

The expected proportion of cases in the reference population ($E(P_i)$) is given by

$$E(P_i) = \frac{Expected\ total\ number\ of\ \ cases\ \ in\ reference\ population}{Total\ number\ of\ \ discharges\ in\ reference\ population} = \frac{\sum_{j=1}^{k} p_{ij} N_j}{N} \quad (4.15)$$

While the expected DOTs/LOT ratio ($E(DL_i)$) in the reference population is given by

$$E(\mathrm{DL}_i) = \frac{\textit{Expected total number of DOTs in reference population}}{\textit{Expected total number of LOT in reference population}} = \frac{\sum_{j=1}^{k} \frac{d_{ij}}{n_{ij}} N_j}{\sum_{j=1}^{k} \frac{l_{ij}}{n_{ij}} N_j} \quad (4.16)$$

These expected values can be compared to their observed counterparts and the respective E/O ratios can be obtained as shown in Table 4.3.

Multiplying the above three equations together

$$\frac{\sum_{j=1}^{k} p_{ij} N_j}{N} \times \frac{\sum_{j=1}^{k} \frac{l_{ij}}{n_{ij}} N_j}{\sum_{j=1}^{k} p_{ij} N_j} \times \frac{\sum_{j=1}^{k} \frac{d_{ij}}{n_{ij}} N_j}{\sum_{j=1}^{k} \frac{l_{ij}}{n_{ij}} N_j} = \frac{\sum_{j=1}^{k} \frac{d_{ij}}{n_{ij}} N_j}{N} = (DSR_i)_{D/D} \quad (4.17)$$

Therefore, the product of the three expected (i.e., adjusted) components is the DSR measured in DOTs/1000 discharges. Figure 4.3 depicts the DSRs along with expected values of the three components for the 70 hospitals. Hospital #4 had the highest DSR followed by Hospital #28 and Hospital #27 while Hospital #59 had the lowest DSR followed by Hospital #6. In addition to facilitating the interhospital comparison of risk-adjusted AbC rates, this figure allows hospitals to compare the magnitude of the individual components that compose these rates with their peers. Moreover, it enables hospitals to determine the relative contribution of each of the three components to their adjusted AbC rates. For example, the figure

shows that, despite having a low DSR, adjusted DOTs/LOT ratio and adjusted proportion of cases, Hospital #31 has a notably high adjusted LOT/case. On the other hand, Hospital #13 which has an above average DSR and adjusted proportion of cases and a high adjusted DOTs/LOT ratio, has a notably low adjusted LOT/case.

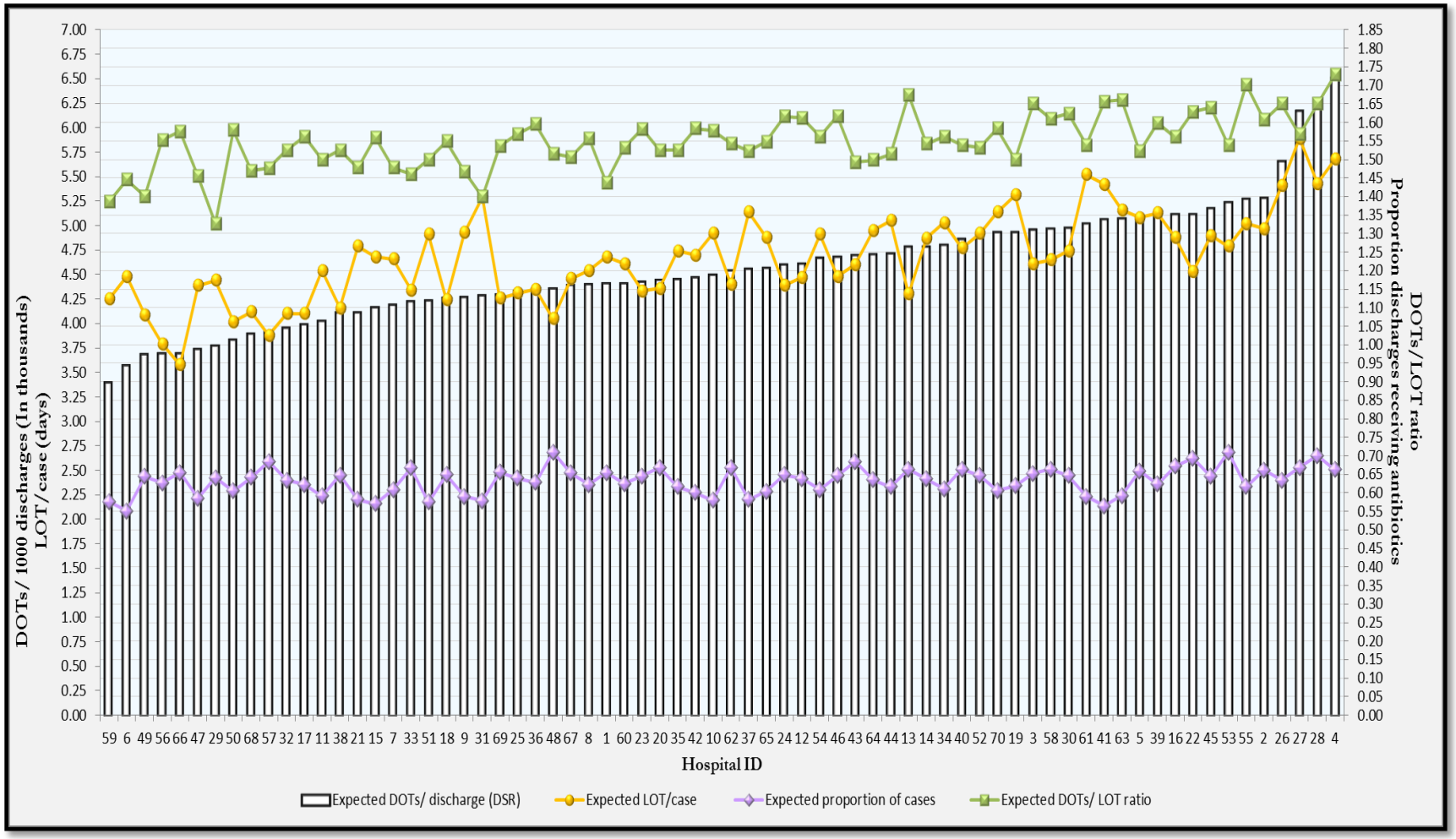


Figure 4.3 Directly Standardized rates (DSRs) of antibacterial drug consumption measured in DOTs/1000 discharges along with the directly standardized (i.e., adjusted) values of the components that compose them at 70 US academic medical centers in 2009. In addition to providing hospitals with a tool to compare their risk-adjusted hospital-wide antibacterial drug consumption rates with those of their peers, this graph also allows the interhospital comparison of the risk-adjusted hospital-wide antibacterial consumption components. This will enable antimicrobial stewardship programs to identify the component(s) where interventions are likely to be the most beneficial.

The mean E/O ratio was 1.02 (SD, 0.13) while the mean O/E ratio was 1.00 (SD, 0.14). The upper and lower critical E/O ratios corresponding to a *z*-score of ±1.96 were (0.76, 1.28) while those corresponding to a *z*-score of ±1.64 were (0.80, 1.24). The corresponding critical values for the O/E ratios were (0.72, 1.27) and (0.77, 1.23), respectively. Hospitals whose E/O (O/E) ratios fell above the upper or below the lower corresponding critical values were identified as outliers at the respective confidence level.

Table 4.5 lists hospital-wide AbC rankings and outlier statuses for the different measures and risk-adjustments methods. Outliers at the 95% confidence level are displayed in red text while outliers at the 90% confidence level are in displayed in blue text. The table shows that there is a general agreement in identifying outliers between the two standardization methods as well as between the two regression models while the agreement between either standardization method and Model II is to a lesser extent.

The weighted κ measures the degree of interrater agreement on a variable that is measured on an ordinal scale by assigning more weight to the agreement when the categories or rankings are close to each other [101]. The most commonly used weights are the linear and the quadratic ones. The former were used to calculate the weighted κ in this study. Further details

on how the SAS PROC FREQ procedure computes weighted κ coefficients and the associated confidence interval (CI) are found in the SAS user's guide (http://support.sas.com/documentation/cdl/en/statug/63033 HTML/default/viewer.htm#statug_freq_a0000000647.htm ; accessed on 20 February 2012).

The weighted κ matrix is presented in Table 4.6 while an interpretation of the κ values as proposed by Altman is shown in Table 4.7 [100]. According to these guidelines, there was a very good agreement in the ranking of hospitals between direct and indirect standardization (weighted κ = 0.85) as well as between the two regression models (weighted κ = 0.91). The agreement between Model II and either direct or indirect standardization was moderate (weighted κ = 0.46 and 0.44, respectively) while there was a moderately good agreement between the observed DOTs/1000 discharges and DOTs/1000 PDs rates (weighted κ = 0.61).

Table 4.5 Hospital Rankings and Outlier Statuses Based on Different Antibacterial Consumption Measures and Risk-adjustment Methods

			Regression		Standardization					Regression		Standardization	
			Model II	Model I	Direct	Indirect				Model II	Model I	Direct	Indirect
Hospital ID	Observed DOTs/1000 Discharges	Observed DOTs/1000 PDs	R-student (DOTs/1000 Discharges)	R-student (DOTs/1000 PDs)	E/O ratio	O/E ratio	Hospital ID	Observed DOTs/1000 Discharges	Observed DOTs/1000 PDs	R-student (DOTs/1000 Discharges)	R-student (DOTs/1000 PDs)	E/O ratio	O/E ratio
1	4638 (44)	863 (47)	-0.589 (20)	-0.533 (22)	0.970 (26)	0.955 (30)	36	3819 (14)	709 (10)	-0.636 (16)	-0.673 (16)	0.959 (25)	0.938 (26)
2	5434 (64)	970 (65)	0.789 (60)	0.845 (58)	1.174 (66)	1.165 (65)	37	4541 (39)	801 (30)	0.121 (40)	0.065 (37)	1.036 (42)	0.959 (31)
3	4371 (33)	812 (34)	-0.496 (23)	-0.409 (26)	1.092 (52)	1.066 (51)	38	3745 (12)	714 (11)	-1.174 (7)	-1.221 (8)	0.907 (15)	0.882 (14)
4	6569 (68)	1088 (69)	**3.289 (70)**	**3.008 (69)**	**1.435 (70)**	**1.455 (70)**	39	4858 (48)	824 (37)	0.530 (54)	0.493 (53)	1.124 (58)	1.111 (60)
5	5638 (67)	894 (56)	0.642 (57)	0.435 (49)	1.129 (60)	1.101 (57)	40	4913 (51)	936 (61)	0.316 (46)	0.465 (52)	1.071 (48)	1.064 (50)
6	2936 (3)	620 (3)	-0.949 (9)	-1.254 (7)	0.811 (2)	**0.725 (1)**	41	4997 (52)	929 (60)	0.506 (53)	0.633 (55)	1.115 (56)	1.106 (59)
7	4070 (22)	769 (21)	-0.509 (22)	-0.529 (23)	0.937 (18)	0.933 (22)	42	4123 (25)	724 (15)	-1.085 (8)	-1.126 (9)	0.984 (31)	0.940 (27)
8	4886 (49)	888 (54)	0.681 (58)	0.694 (56)	0.980 (30)	1.019 (41)	43	3949 (18)	788 (25)	0.110 (39)	0.132 (39)	1.069 (47)	1.039 (46)
9	4236 (29)	725 (16)	-1.635 (3)	-1.641 (3)	0.943 (20)	0.935 (24)	44	5055 (55)	863 (48)	-0.366 (27)	-0.384 (27)	1.038 (43)	1.036 (45)
10	4622 (42)	812 (35)	-0.195 (32)	-0.230 (32)	0.999 (34)	0.997 (35)	45	5301 (61)	943 (63)	**1.670 (66)**	**1.714 (67)**	1.148 (63)	1.143 (64)
11	4115 (24)	796 (27)	0.398 (50)	0.456 (51)	0.889 (13)	0.887 (15)	46	4895 (50)	940 (62)	0.851 (61)	1.077 (62)	1.030 (40)	1.023 (42)
12	5160 (59)	922 (59)	-0.195 (33)	-0.045 (35)	1.014 (38)	1.000 (36)	47	3855 (15)	701 (8)	-0.869 (11)	-0.951 (11)	0.841 (6)	**0.756 (3)**
13	4685 (47)	890 (55)	0.989 (62)	1.181 (63)	1.058 (45)	1.036 (44)	48	2522 (1)	720 (14)	1.585 (64)	1.461 (66)	0.974 (27)	1.025 (43)
14	4298 (32)	771 (22)	-0.624 (17)	-0.597 (18)	1.056 (44)	1.047 (48)	49	3125 (4)	648 (4)	-0.818 (12)	-1.054 (10)	0.820 (5)	0.809 (5)
15	4514 (37)	814 (36)	-0.797 (14)	-0.754 (14)	0.917 (16)	0.895 (16)	50	3648 (9)	802 (32)	-0.156 (34)	-0.042 (36)	0.859 (8)	0.837 (7)
16	5449 (65)	906 (57)	0.539 (55)	0.411 (48)	1.125 (59)	1.125 (62)	51	4656 (45)	786 (24)	-0.620 (19)	-0.594 (19)	0.932 (17)	0.931 (21)
17	3902 (16)	715 (12)	-1.268 (5)	-1.283 (5)	0.880 (10)	0.870 (12)	52	5042 (54)	801 (31)	0.291 (45)	0.166 (42)	1.091 (51)	1.104 (58)
18	3917 (17)	698 (7)	-1.260 (6)	-1.281 (6)	0.937 (19)	0.946 (29)	53	5624 (66)	871 (50)	0.354 (49)	0.139 (40)	1.169 (65)	1.197 (66)
19	4205 (27)	719 (13)	-0.624 (18)	-0.675 (15)	1.094 (54)	1.077 (54)	54	5033 (53)	845 (43)	-0.714 (15)	-0.665 (17)	1.029 (39)	1.006 (39)
20	4627 (43)	834 (39)	-1.462 (4)	-1.294 (4)	0.978 (29)	0.928 (20)	55	5266 (60)	910 (58)	1.442 (63)	1.396 (65)	1.160 (64)	1.137 (63)
21	4605 (41)	799 (29)	-0.811 (13)	-0.793 (13)	0.906 (14)	0.874 (13)	56	3725 (10)	780 (23)	-0.311 (29)	-0.245 (31)	0.815 (4)	0.820 (6)
22	5376 (62)	1034 (68)	**1.767 (67)**	**2.068 (68)**	1.129 (61)	1.114 (61)	57	3953 (19)	840 (42)	0.288 (44)	0.439 (50)	0.864 (9)	0.850 (9)
23	4245 (30)	847 (44)	0.191 (41)	0.271 (45)	0.976 (28)	0.980 (34)	58	5063 (57)	840 (41)	-0.010 (37)	-0.073 (34)	1.094 (53)	1.071 (52)
24	4665 (46)	953 (64)	0.471 (52)	0.863 (59)	1.013 (37)	1.003 (37)	59	3408 (5)	592 (2)	**-1.840 (2)**	**-1.877 (2)**	**0.760 (1)**	**0.741 (2)**
25	4408 (35)	852 (45)	-0.395 (26)	-0.314 (29)	0.952 (23)	0.937 (25)	60	4161 (26)	811 (33)	0.080 (38)	0.077 (38)	1.003 (35)	0.978 (33)
26	5387 (63)	1026 (67)	**2.969 (69)**	**3.261 (70)**	**1.282 (67)**	**1.239 (67)**	61	3759 (13)	791 (26)	0.354 (48)	0.402 (47)	1.137 (62)	0.860 (10)
27	6716 (69)	989 (66)	1.587 (65)	0.978 (61)	**1.391 (69)**	**1.369 (68)**	62	4079 (23)	760 (19)	-0.293 (30)	-0.370 (28)	1.031 (41)	1.004 (38)
28	7580 (70)	1104 (70)	**2.111 (68)**	1.322 (64)	**1.381 (68)**	**1.391 (69)**	63	5056 (56)	864 (49)	0.207 (42)	0.173 (43)	1.115 (57)	1.083 (56)
29	3479 (6)	561 (1)	**-2.951 (1)**	**-2.745 (1)**	0.850 (7)	0.842 (8)	64	4228 (28)	746 (17)	-0.475 (24)	-0.554 (20)	1.059 (46)	1.061 (49)
30	5120 (58)	861 (46)	0.429 (51)	0.349 (46)	1.094 (55)	1.044 (47)	65	4538 (38)	886 (53)	-0.063 (36)	0.159 (41)	1.007 (36)	1.008 (40)
31	3953 (20)	695 (6)	-0.872 (10)	-0.892 (12)	0.950 (22)	0.933 (23)	66	3733 (11)	756 (18)	-0.569 (21)	-0.550 (21)	0.813 (3)	0.787 (4)
32	3510 (7)	703 (9)	-0.082 (35)	-0.171 (33)	0.884 (11)	0.866 (11)	67	3991 (21)	876 (52)	0.628 (56)	0.840 (57)	0.999 (33)	0.965 (32)
33	4276 (31)	829 (38)	-0.348 (28)	-0.314 (30)	0.958 (24)	0.912 (17)	68	3594 (8)	836 (40)	0.336 (47)	0.507 (54)	0.885 (12)	0.915 (18)
34	4554 (40)	797 (28)	0.249 (43)	0.202 (44)	1.089 (50)	1.079 (55)	69	4379 (34)	873 (51)	0.698 (59)	0.896 (60)	0.946 (21)	0.924 (19)
35	2896 (2)	654 (5)	-0.277 (31)	-0.505 (24)	0.995 (32)	0.942 (28)	70	4459 (36)	765 (20)	-0.443 (25)	-0.440 (25)	1.086 (49)	1.073 (53)

Table 4.6 Weighted Kappa Coefficients and Associated 95% Confidence Intervals Measuring the Agreement Between Different Risk-adjustment Methods in Ranking Antibacterial Drug Consumption

	Observed		Regression		Standardization	
	DOTs/1000 Discharges (1)	DOTs/1000 PDs (2)	Model II (3)	Model I (4)	Direct (5)	Indirect (6)
(1)		0.61 (0.52, 0.70)	0.39 (0.25, 0.52)	-	0.59 (0.48, 0.70)	0.61 (0.50, 0.71)
(2)			-	0.59 (0.49, 0.70)	-	-
(3)				0.91 (0.88, 0.93)	0.46 (0.33, 0.59)	0.44 (0.31, 0.57)
(4)					-	-
(5)						0.85 (0.78, 0.92)
(6)						

Table 4.7 Guidelines for the Interpretation of Kappa Scores [100]

Kappa	Interpretation
< 0.20	Poor agreement
0.21-0.40	Fair agreement
0.41-0.60	Moderate agreement
0.61-0.80	Good agreement
0.81-1.00	Very good agreement

4.2.3 Comparison of Interhospital Antibacterial Drug Consumption at the CSL Level

The relative internal homogeneity of strata is a necessary assumption of standardization and other stratified analysis methods. For this assumption to hold, the variability within the same stratum should be less than that between different strata [102]. If this assumption is valid, then the direct comparison of observed CSL-specific rates would seem reasonable. It is worth mentioning that the CSL-specific O/E ratios obtained from indirect standardization are identical to the CSL-specific E/O ratios obtained from direct standardization as both represent the ratio of the observed CSL-specific rates in the study populations to the corresponding rates in the reference population. Therefore, within the same CSL, the interhospital comparison of CSL-specific E/O or O/E ratios is the same as the comparison of the observed CSL-specific rates measured in DOTs/1000 discharges.

Figures 4.4, 4.5, 4.6 and 4.7 represent interhospital comparisons of AbC rates - measured in both DOTs/1000 discharges and DOTs/1000 PDs and ordered from lowest to highest consumption- and their associated components within 4 representative CSLs. The ventilator support CSL is representative of CSLs that have patient populations with complex clinical profiles and high SOI (e.g., transplant CSLs). Such CSLs typically have high

AbC but exhibit very little interhospital variability in the proportion of cases since nearly all patients receive antimicrobial therapy (Figure 4.4). However, the variability in the other components is quite high and the high variability in LOS may explain why the agreement between the two AbC rates in ranking hospitals within the ventilator support CSL is only fair (weighted κ = 0.32, 95% CI (0.17-0.47)).

Figures 4.5 represents a comparison of interhospital AbC within the general medicine CSL. This CSL represents CSLs that may have a relatively heterogeneous patient mix and moderate AbC. These CSLs typically exhibit little interhospital variability in the components of AbC as shown in the figure (Note that this figure is drawn to the same scale as Figure 4.6 and Figure 4.7 which is different from that of Figure 4.4). The agreement between the two AbC rates within the general medicine CSL was moderate (weighted κ = 0.52, 95% CI (0.40-0.64)). Other CSLs that have a similar pattern of use include, among others, the gastroenterology and orthopedics CSLs.

The gynecology CSL (Figure 4.6), on the other hand, is a fairly homogenous CSL with a relatively low AbC. However, it has an exceptionally high interhospital variability in the proportion of cases as shown in the figure. The agreement between the two AbC rates within this CSL was fair (weighted κ = 0.40, 95% CI (0.26-0.55)). Finally, Figure 4.7 represents the

interhospital comparison of AbC within the psychiatry CSL. This CSL is characterized by very low AbC but a high interhospital variability in LOT/case and LOS relative to the average values of these components. The agreement between the two AbC rates within this CSL was fair to moderate (weighted κ = 0.41, 95% CI (0.27-0.56)).

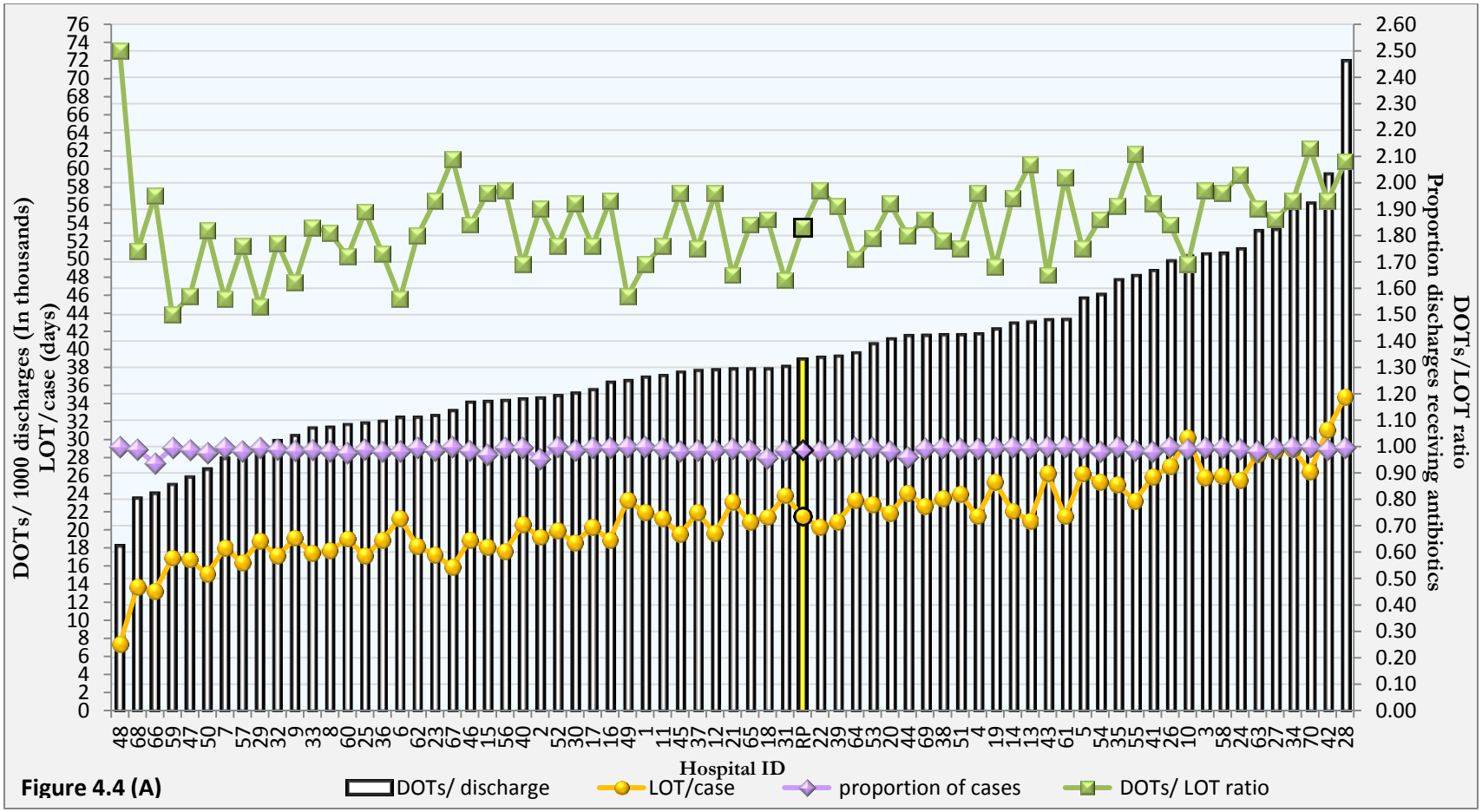


Figure 4.4 A comparison of interhospital antibacterial drug consumption, measured in DOTs/1000 discharges (Figure A) and DOTs/1000 patient days (figure B), along with the associated components of consumption within the ventilator support clinical service line (CSL) in 70 U.S. academic medical centers during 2009. The yellow bar represents the reference population (RP) and the black-bordered components represent the components of RP. The very high proportion of cases with very low interhospital variability is typical of high consumption CSLs which include, in addition to ventilator support, the transplant CSLs. However, these CSLs exhibit high variability in the other components and the high variability in the length of stay (LOS) may explain why the agreement between the two antibacterial consumption rates is only fair.

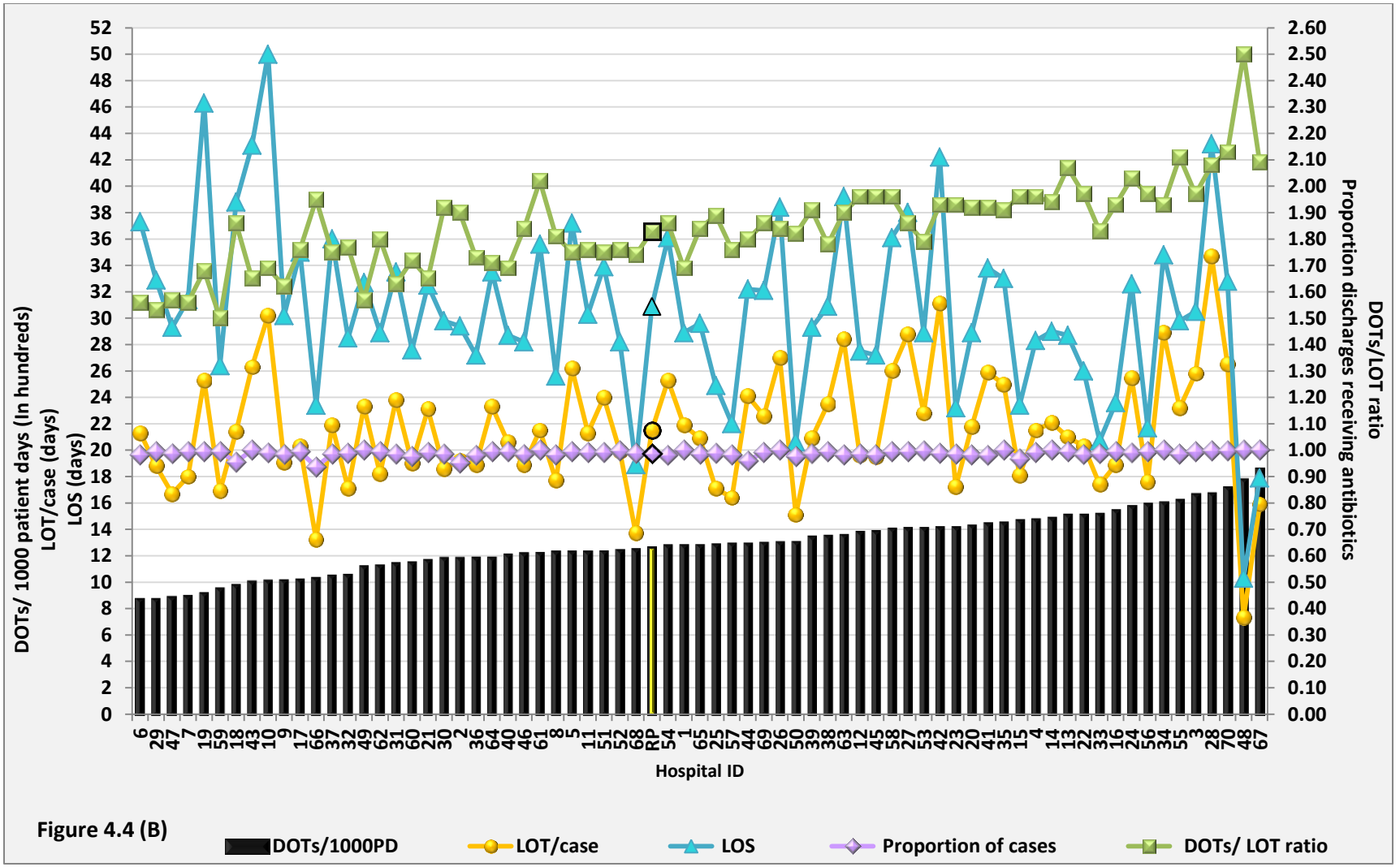


Figure 4.4 (B)

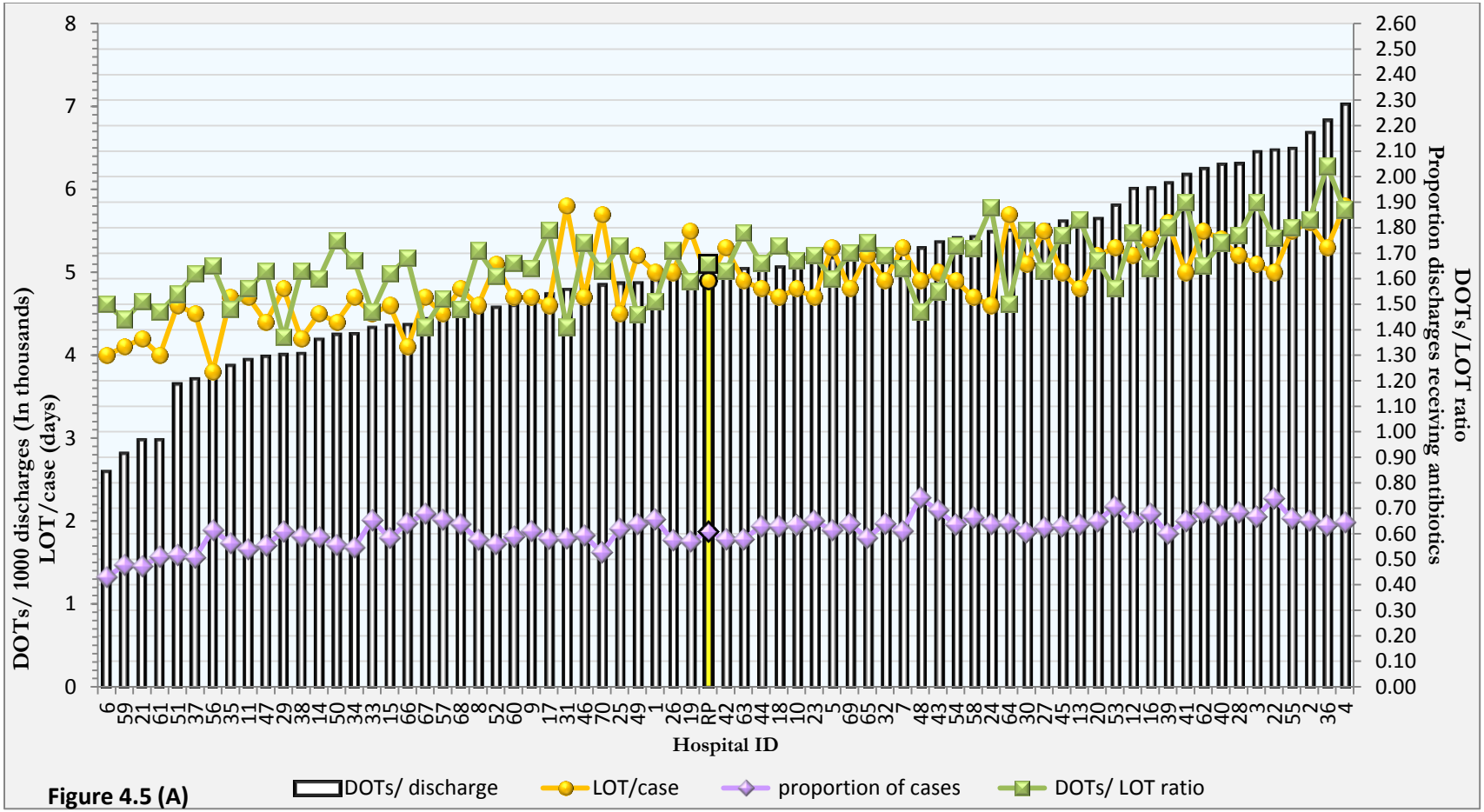


Figure 4.5 A comparison of interhospital antibacterial drug consumption, measured in DOTs/1000 discharges (upper figure) and DOTs/1000 patient days (lower figure), along with the associated components of consumption within the general medicine clinical service line (CSL) in 70 U.S. academic medical centers during 2009. This CSL exhibits moderate consumption with relatively low interhospital variability in the components of consumption despite its relatively heterogeneous patient-mix. Other examples of CSLs with similar use pattern include orthopedics and gastroenterology.

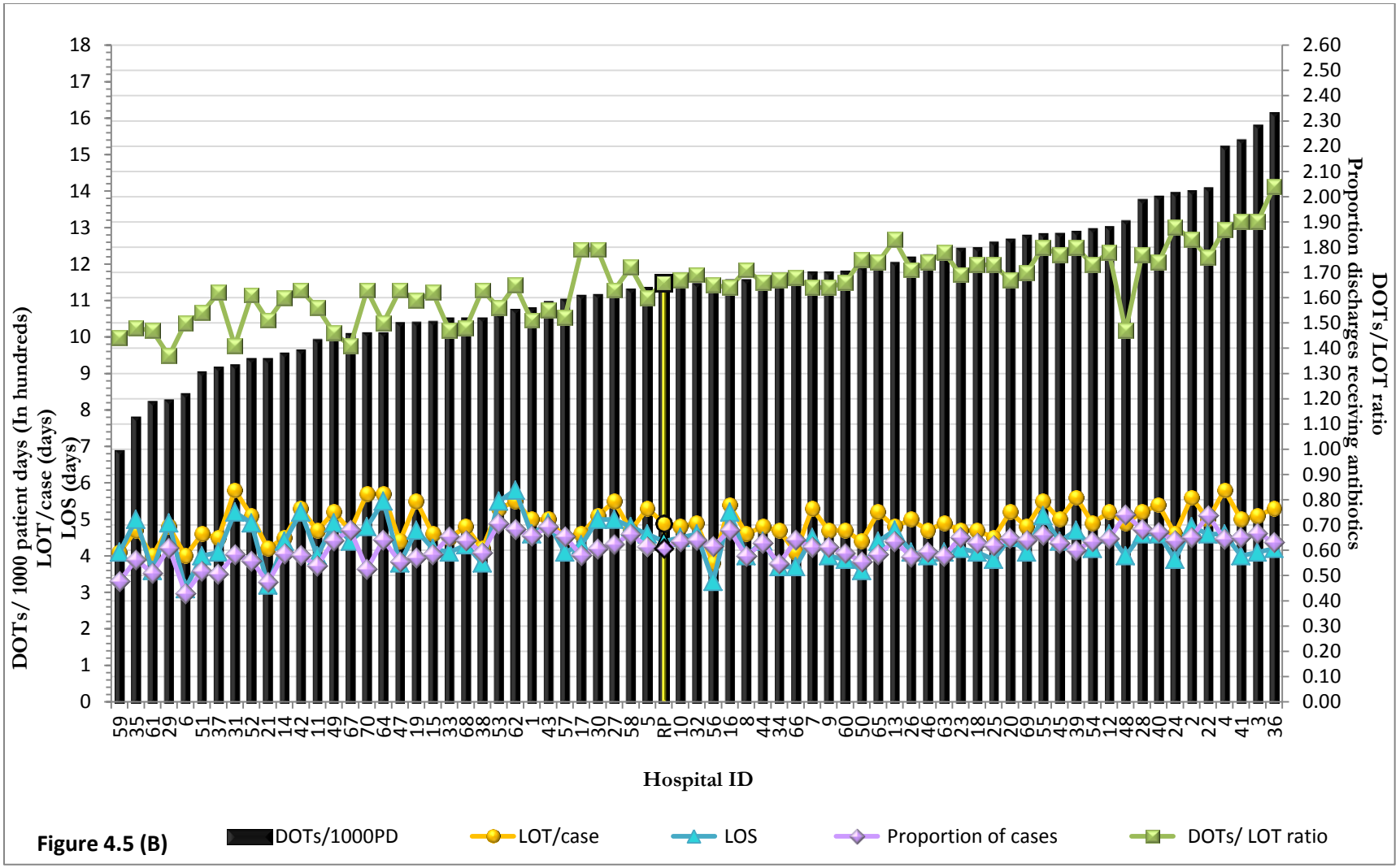


Figure 4.5 (B)

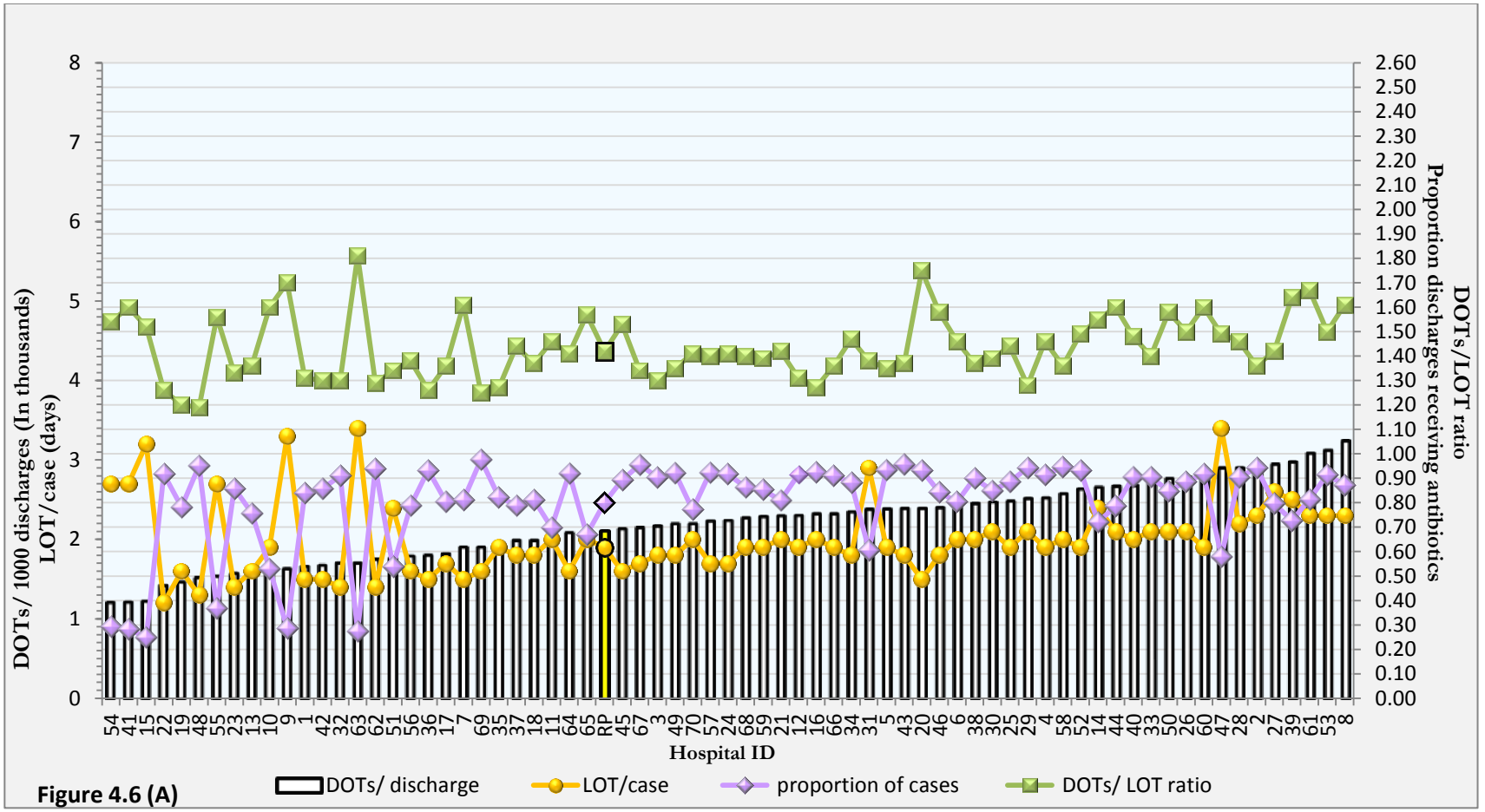


Figure 4.6 A comparison of interhospital antibacterial drug consumption, measured in DOTs/1000 discharges (Figure A) and DOTs/1000 patient days (figure B), along with the associated components of consumption within the gynecology clinical service line (CSL) in 70 U.S. academic medical centers during 2009. This CSL is characterized by a moderately low antibacterial consumption with a notably high variability in the proportion of cases.

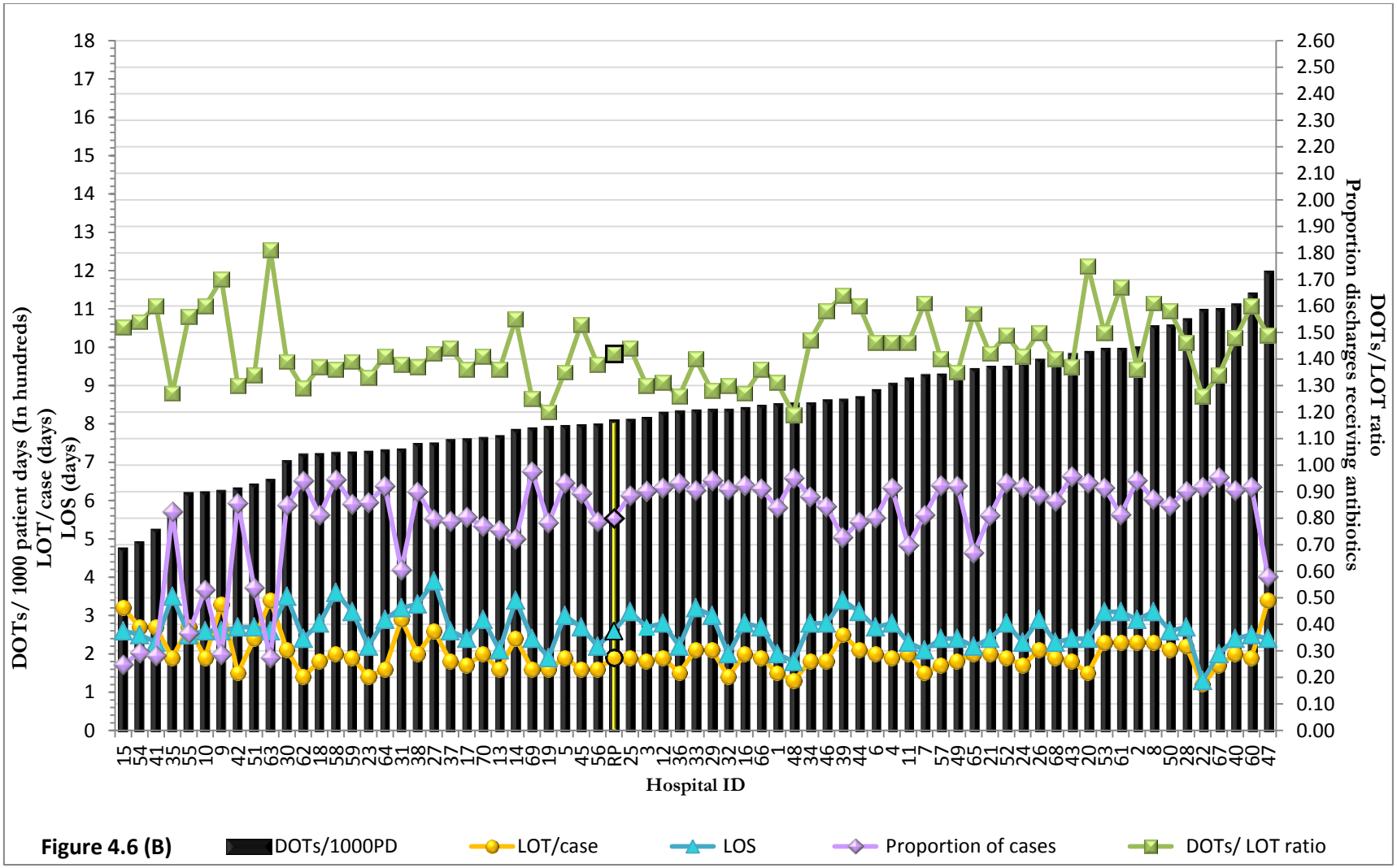


Figure 4.6 (B)

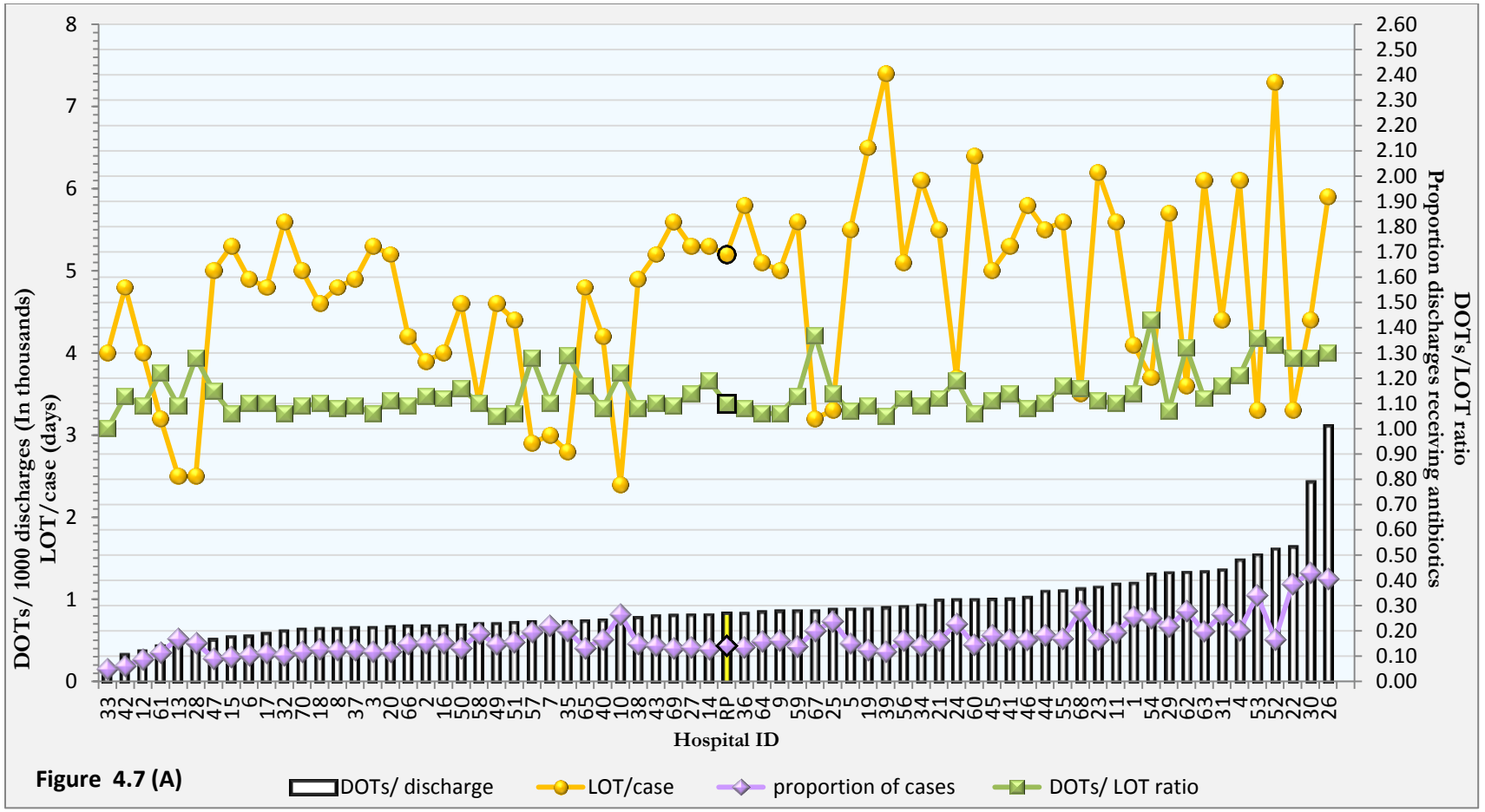


Figure 4.7 A comparison of interhospital antibacterial drug consumption, measured in DOTs/1000 discharges (Figure A) and DOTs/1000 patient days (figure B), along with the associated components of consumption within the psychiatry clinical service line (CSL) in 70 U.S. academic medical centers during 2009. This CSL is characterized by very low antibacterial consumption but the variability in the components of consumption; namely LOT/case and LOS, is high relative to the average value of these components.

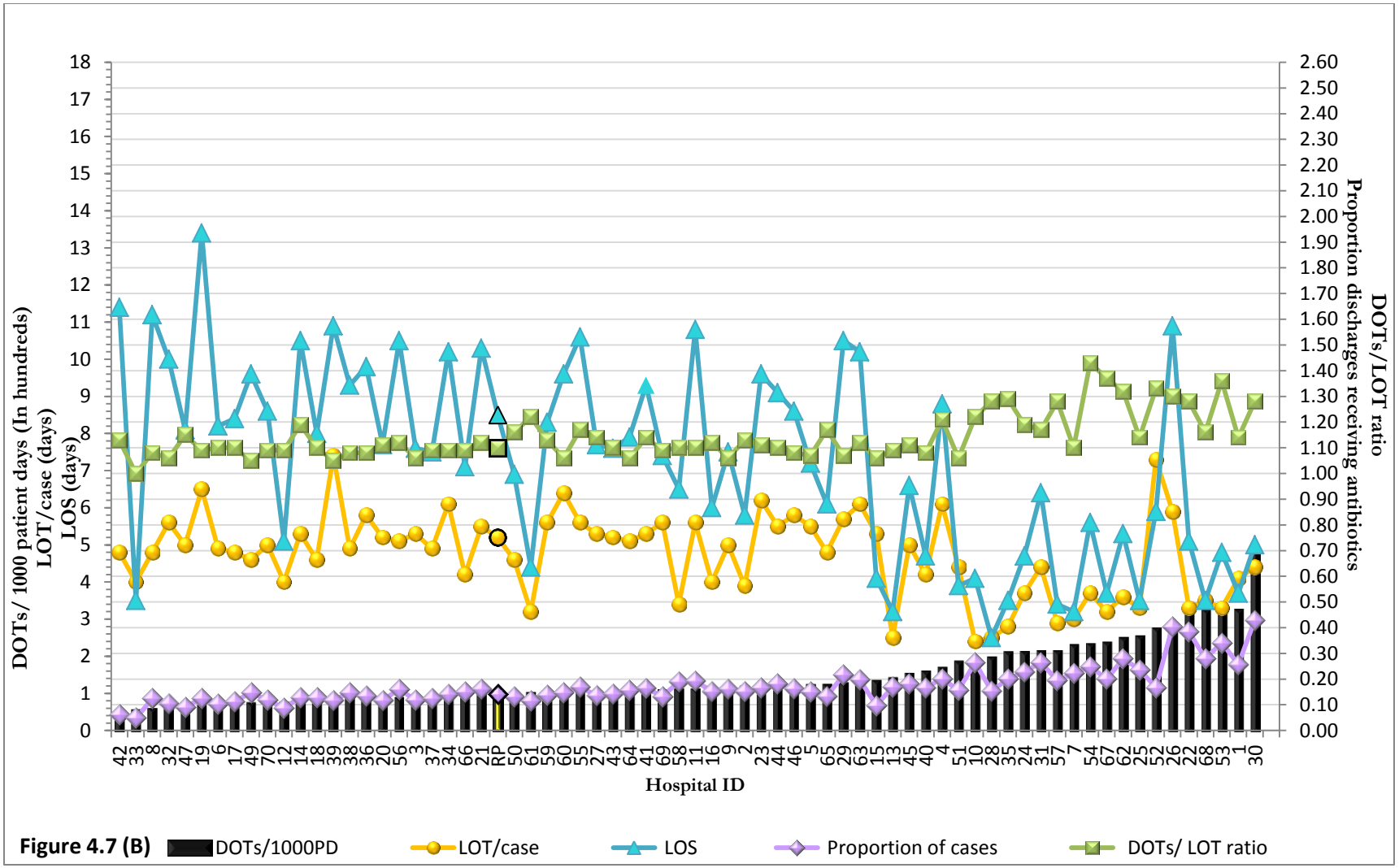


Figure 4.7 (B)

Figure 4.8 and Figure 4.9 represent the CSL-specific O/E ratios for the DOTs/1000 discharges rate and its 3 associated components in Hospital #13 and Hospital #31 in Figure 4.3, respectively. As previously shown in Figure 4.3, the risk-adjusted hospital-wide values of Hospital #13 were above average for the DOTs/1000 discharges rate and the proportion of cases, high for DOTs/LOT ratio and low for LOT/case. The CSL-specific O/E ratios in Figure 4.8 are in general agreement with this hospital-wide pattern as explained in the figure legend. Figure 4.3 also showed that the risk-adjusted hospital-wide values of Hospital #31 were low for the DOTs/1000 discharges rate, the proportion of cases and the DOTs/LOT ratio but notably high for LOT/case. Figure 4.9 shows a very clear agreement with this hospital-wide pattern.

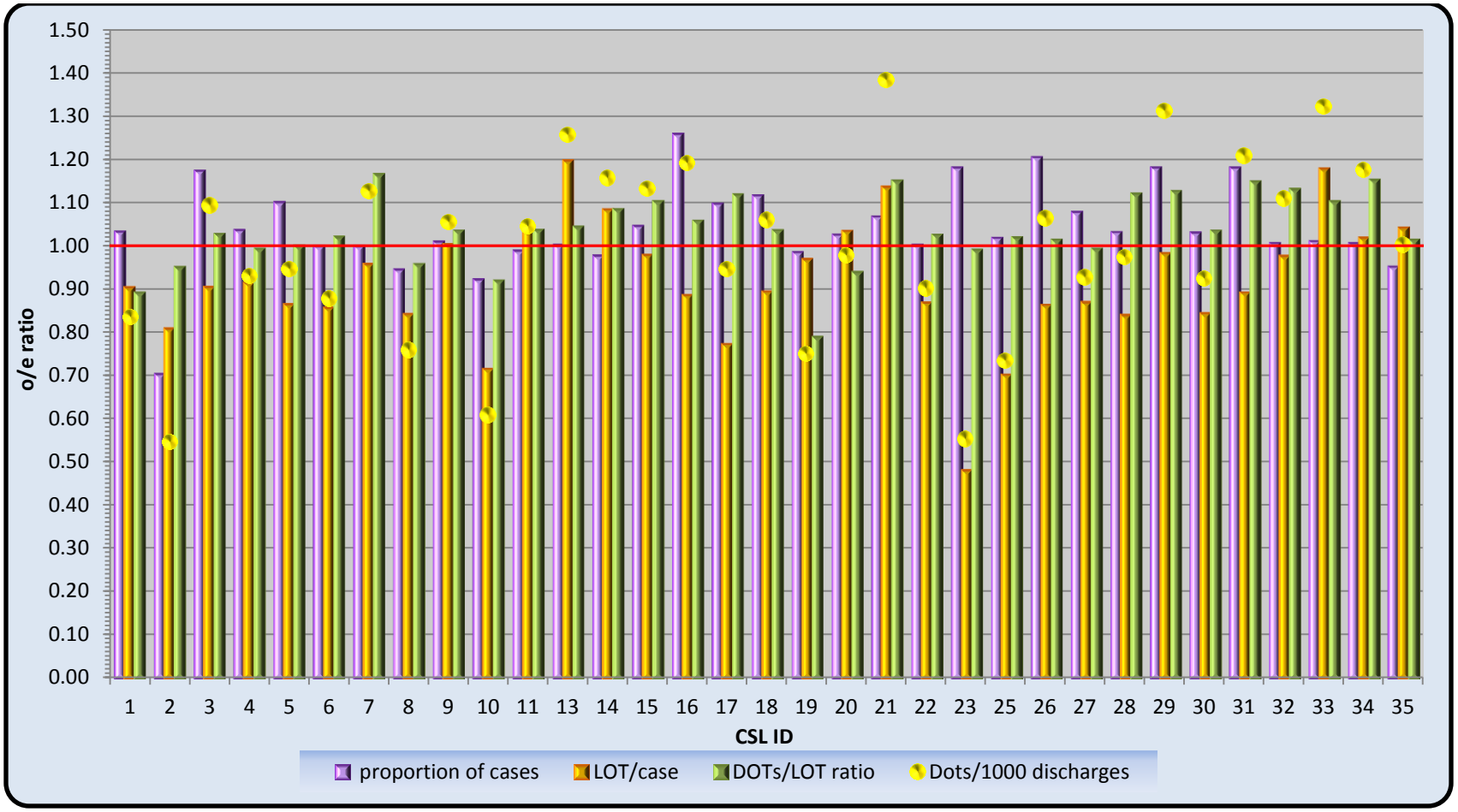


Figure 4.8 Observed to expected (O/E) ratios for antibacterial drug consumption (DOTs/1000 discharges) and its associated components in 33 clinical service lines (CSLs) that compose hospital #13. This hospital had no patients in the liver transplant (CSL #12) or rehabilitation (CSL #24) CSLs. The O/E ratios for DOTs/1000 discharges are represented by the yellow spheres for clarity while the red dotted line represents an O/E ratio value of 1.00. The above figure shows that the CSL-specific O/E ratios for LOT/case were higher than 1.00 in 8 of the 33 CSLs only (compared to 23 CSLs for DOTs/LOT ratio and 22 CSLs for the proportion of cases) and that the LOT/case had the lowest O/E ratio among the 3 components in 22 of the 33 CSLs that compose this hospital. This CSL-specific pattern is in general agreement with the hospital-wide one illustrated in Figure 4.3.

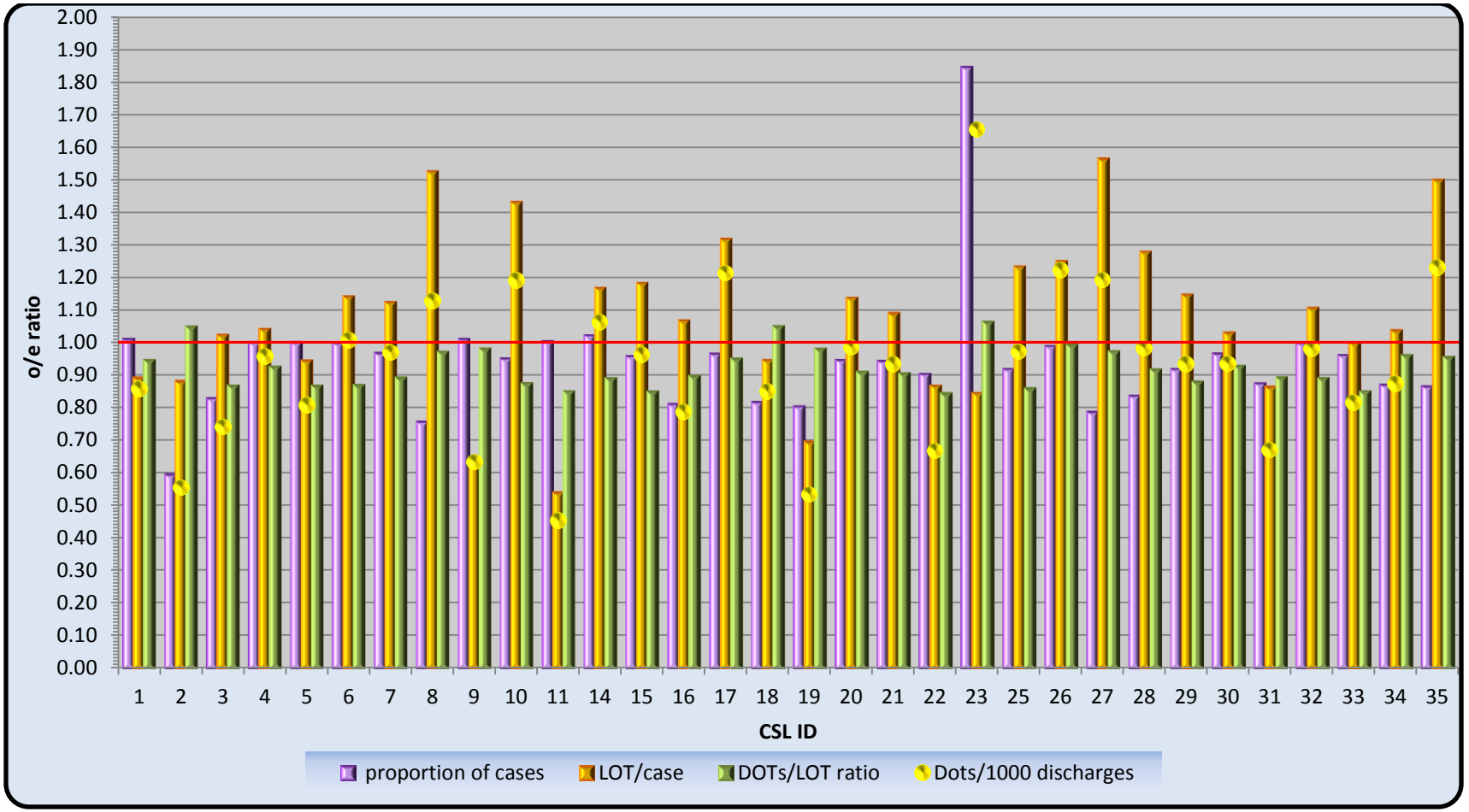


Figure 4.9 Observed to expected (O/E) ratios for antibacterial drug consumption (DOTs/1000 discharges) and its associated components in 32 clinical service lines (CSLs) that compose hospital #31. This hospital had no patients in the liver transplant (CSL #12), lung transplant (CSL #13) or rehabilitation (CSL #24) CSLs. As shown in Figure 4.3, this hospital had a notably high risk-adjusted hospital-wide LOT/case despite having low risk-adjusted hospital-wide DOTs/1000 discharges rate, DOTs/LOT ratio and proportion of cases. This is in agreement with the above figure which clearly shows that, with the notable exception the psychiatry CSL (CSL #23), antibacterial consumption in high consumption CSLs can be attributed to high LOT/case values.

Chapter V
Discussion, Conclusion and Future Directions

5.1 Summary of Findings and Study Strengths

The need for the development of risk-adjusted AbC benchmarks in hospitals has been advocated by prominent ID societies [2]. The ID community responded and important advances have been made in benchmarking AbC in Europe [5,7,8] and the US [6,9]. However, benchmarking AbC is still in its infancy and much work remains to be done [29].

Regression modeling has been the standard methodology for benchmarking AbC [5-7]. Recently however, indirect standardization emerged as a viable and appealing alternative for this purpose [8,9]. Direct standardization is a closely related risk-adjustment method that may be advantageous to indirect standardization for benchmarking purposes as it allows the direct comparison of risk-adjusted rates. However, direct standardization has not been previously applied to benchmark AbC.

The current investigation applied both direct and indirect standardization to the benchmarking of adult AbC in 70 US academic medical centers. In addition, this investigation used regression modeling as a means of explaining the interhospital variability in AbC, measured in DOTs/1000 PDs and DOTs/1000 discharges, using LOS, the CMI, bed size and the infection, surgery and transplant rates as potential predictor variables. Finally, a comparison was made between the two standardization methods, the two regression models and between direct standardization and either regression model with respect to their agreement in ranking hospitals according to their risk-adjusted AbC as well as in identifying outlier hospitals.

When AbC was measured in DOTs/1000 discharges, the "best" model included LOS, infection rate and transplant rate as predictor variables and was able to explain 64% of the variability in interhospital AbC. This is in agreement with the results of an investigation in a sample of private hospitals in France which reported that a linear regression model that included LOS, the existence of an ID consultant, the proportion of PDs in the medical ward and the proportion of PDs in surgery as predictor variables, explained 68% of AbC measured in DDD/100 admissions [5]. When AbC was measured using DOTs/1000 PDs, the model selection criteria selected the model with infection rate and transplant rate as predictor variables. The model only explained 31% of the variability in AbC

between hospitals. This result is in agreement with MacDougal and Polk who reported the same percentage of explained variability using a model that included hospital size, the number of ICU days, surgical volume, and the number of cases of bacteremia, pneumonia, and UTI as predictors of total AbC measured in DOTs/1000 PDs in a sample of US hospitals [6]. However, the above French investigation was able to explain a much higher percentage (84%) of the variability in AbC measured in DDD/1000 PDs in a sample of public non-teaching hospitals using the existence of an ID consultant and the proportion of PDs in medical and surgical wards and ICUs as predictor variables. The agreement between the two regression models in ranking hospitals and identifying high and low outliers was very good in the current investigation.

The direct standardization method produced E/O ratios that ranged from 0.76 to 1.44 while the O/E ratios obtained from indirect standardization ranged from 0.73 to 1.45. The agreement between the 2 methods in ranking hospitals and identifying outliers was very good. On the other hand, the agreement between either method and the regression model that used DOTs/1000 discharges as the outcome was moderate. The agreement between observed and risk-adjusted AbC ranged from fair to good depending on the risk-adjustment methodology. A recent investigation that used a combination of regression modeling and indirect standardization to

risk adjust hospital AbC in Finland found that hospital rankings according to their observed AbC rates did not match their risk-adjusted rankings in 25 out of 30 hospitals [8]. However, while the study used percent agreement, I used weighted kappa to measure the agreement between observed and risk-adjusted rankings.

In addition to deriving risk-adjusted AbC rates (DSRs), this investigation used direct standardization to risk-adjust the hospital-wide components of AbC including the proportion of discharges receiving antibiotics, LOT/discharge for patients receiving antibacterial therapy and DOTs/LOT ratio. These components have been recently used to benchmark AbC in hospitals at the CSL level [9]. However, this investigation provides hospitals with a strategy to benchmark both their AbC rates as well as the components of AbC with their peers at the hospital level. This is especially useful since the DOTs/1000 discharges measure is the product of the three above-mentioned components. Hospitals can also use this strategy to identify which component or combination of components is contributing the most to their hospital-wide AbC. This strategy does not focus on hospitals that are outliers in their AbC rates only. Non-outlier hospitals with respect to their AbC rates could also benefit from this strategy as they may have a high or an outlier value for one or more of these components. Hospitals can devise hospital-wide intervention strategies to address the most problematic

component(s). Obviously, benchmarks at the CSL or unit level are still needed as some CSLs/units will inevitably deviate from the general hospital-wide use pattern.

Another important strength of this study is that it demonstrated that the DOTs/1000 discharges measure is better correlated than DOTs/1000 PDs with non-modifiable factors such as LOS, infection and transplant rates as well as with factors that are amenable to intervention such as the proportion of discharges receiving antibacterial therapy, LOT/discharge for patients receiving antibacterial therapy and the DOTs/LOT ratio. In fact, these three components explained 99% of the variability in AbC in the 70 hospitals when consumption was measured in DOTs/1000 discharges but only 82% of the variability in AbC measured in DOTs/1000 PDs (data not presented). LOT/discharge for patients receiving antibacterial therapy was the component with the strongest univariable correlation with the DOTs/1000 discharges measure ($R^2 = 0.68$) followed by the DOTs/LOT ratio ($R^2 = 0.43$) and the proportion of discharges receiving therapy ($R^2 = 0.20$). Since these components (especially LOT/discharge for patients receiving antibacterial therapy and the proportion receiving antibiotic therapy) are thought to be strongly associated with antimicrobial resistance, this suggests that DOTs/1000 discharges may correlate better with antimicrobial resistance than DOTs/1000 PDs [37]. Accordingly,

benchmarking efforts should express antibiotic use rates using both denominators whenever possible.

Finally, this investigation showed that the variability in AbC rates and their associated components are generally higher in the high consumption CSLs such as the ventilator support and the transplant CSLs than in CSLs where AbC is average or below average such as the general medicine, orthopedics and gastroenterology CSLs. The high variability in the former CSLs may be due to the small number of discharged patients but it may also be due to interhospital differences in SOI or the proportion of inappropriate therapy.

5.2 Limitations

This attempt of benchmarking AbC in a subset of US teaching hospitals is limited by the use of an administrative database that has not been validated for the task at hand. Administrative databases are often used without validation and the accuracy of the information they provide may be considerably inferior to that of prospectively maintained databases [103]. However, variables pertaining to ischemic stroke patients in the UHC database have been previously validated and were found to highly agree with data retrieved from medical records [104,105]. Moreover, a study investigating trends in AbC among UHC hospitals conducted a limited

validation of the number of DOTs for drugs used in the management of *Clostridium difficile* disease in one of the UHC hospitals and found an excellent correlation (R^2=0.99) between UHC data and that extracted locally from medical records [88]. Additionally, some participating hospitals were contacted and asked to provide their internally-generated AbC data (if available). These were compared against the UHC data and significant discrepancies were investigated.

It can be argued that the direct standardization approach adjusts for patient mix in a more accurate manner than the regression modeling approach. However, one limitation of standardization is that it cannot adjust for continuous variables (unless categorized). The CSLs may differ in their SOI, infection rates, and other important predictors of AbC. Also, while some CSLs are composed of a small number of DRGs and are relatively homogenous (e.g., BMT), others are composed of a large number of CSLs and may exhibit some heterogeneity that may contribute to residual confounding (e.g., general medicine). In addition, not all hospitals had the same CSL composition so using a common reference population was not possible. However, the CSLs that were not common to all hospitals had very small weights that the differences between the different reference populations were marginal. Therefore, differences in the CSL composition between hospitals are unlikely to have jeopardized the validity of the results.

Another limitation of this study lies in the assumption that some variables such as infection rates and LOS are exclusively non-modifiable. The total infection rate in a hospital is for the most part a mixture of HAIs which are generally considered to be preventable (i.e., modifiable), and community-acquired infections which are considered non-modifiable from the perspective of hospitals. Length of stay (LOS) may be considered a non-modifiable variable in the sense of being regarded as a surrogate of SOI or as a modifiable factor indicative of the quality of health care. While HAIs cannot be entirely eliminated, they can be significantly reduced by implementing proven infection control measures and strategies [106]. The use of antimicrobials to treat avoidable HAIs may not constitute inappropriate use from a clinical perspective since these antimicrobials are used to treat definitive infections. However, an argument can be made that the use of antimicrobials to treat avoidable HAIs can be avoided as well, and thus, may be considered as inappropriate use. Excluding HAIs from the total infection rate will increase the likelihood of identifying hospitals with high HAIs as being high outliers in terms of their antimicrobial use. Identifying avoidable HAI's is probably best achieved with prospective patient-level data or through dedicated surveillance programs.

It should be emphasized that a relatively low antimicrobial use does not necessarily indicate the presence of an effective ASP. Low antimicrobial

use may be an indication of undertreating infections. It can also be a biased underestimation due to an inherent flaw in the metric used to measure antimicrobial use as previously mentioned. Benchmarking antimicrobial use is just one aspect of measuring the quality of care provided by a hospital's ID team. Benchmarking infection rates, antimicrobial resistance, ASP, and infection control measures are just as important. Linking antimicrobial use benchmarks with these other performance benchmarks is crucial in order to assess the appropriateness of antimicrobial use in hospitals.

5.3 Conclusion

Identifying and effectively reducing inappropriate antimicrobial therapy without compromising patients' well-being is central to the mission of ASPs. However, continuous monitoring of AbC at the patient level is prohibitive for many hospitals. Aggregate-level AbC data measured at the hospital and patient care area levels provide hospitals with a viable alternative for monitoring their AbC and benchmarking it against other hospitals. Indirect standardization has only been recently applied to benchmarking AbC in hospitals. The greatest advantage of this procedure over the more commonly used regression modeling method is its feasibility for risk-adjustment of AbC at both the hospital-wide and the unit or patient care area levels. However, one important limitation is that AbC rates are standardized using the

hospitals' own patient mix distribution and therefore, the direct comparison of indirectly standardized rates is not always valid.

Direct standardization is an alternative and closely related procedure that standardizes AbC rates to a common population mix enabling the direct comparison of interhospital AbC rates. Moreover, this procedure can be applied to standardize other meaningful components of AbC including the proportion of patients receiving antimicrobial therapy and proxy measures for the LOT and the average number of administered agents. Benchmarking these components along with AbC rates will enable hospitals to identify the specific component(s) that contributes the most to their AbC whether at the hospital level, or the unit or patient care area level. Hospitals can then devise strategies that effectively target the identified component(s). Although this investigation found the results of both standardization methods to be similar, this will not always be the case. Direct standardization should be regarded as the preferred method for the interhospital comparison of AbC unless there is some justification for preferring the indirect method such as the small size of strata.

5.4 Future Directions

The benchmarking literature is not extensive nor is it consistent and much work remains to be done and many research opportunities are available. A recent review

of benchmarking antibiotics in hospitals highlighted some of the gaps that need to be filled in the benchmarking literature [29]. Testing the "benchmarking hypothesis" is one area that deserves special consideration. The authors state,

> … Will hospitals respond to risk-adjusted comparative AbC data by implementing strategies and interventions to improve their antibiotic management and prescribing practices? If interventions are made in a number of hospitals, what interventions are most effective and how does AbC change? Will AbC just be shifted to other antimicrobials or will use be substantially reduced? And finally, if AbC is improved, will this be accompanied by important changes in clinical outcomes, including lower rates of antibiotic resistance and infections caused by resistant organisms, including rates of *Clostridium difficile* infection (CDI). Will reduced use be accompanied improved patient outcomes because of lower rates of HAIs caused by resistant organisms? Will the evidence be compelling enough for most hospitals to undertake similar interventions? [29]

The only investigation to test the benchmarking hypothesis is the CDC Project ICARE [87]. This study reported that changes in prescriber practice, motivated by providing hospitals with national AbC benchmarks, were associated with a significant reduction in vancomycin use and a subsequent reduction in the prevalence of vancomycin-resistant enterococci (VRE).

Other areas identified by the above review paper for prospective investigations include benchmarking antimicrobial use in developing countries and pediatric populations in addition to benchmarking antifungal and antiviral drug use. The usefulness of other statistical methods such as Bayesian regression, hierarchical regression and data envelopment analysis for benchmarking AbC is worth exploring. Also, adjusting for SOI within CSLs or hospital units is worth considering as it may provide a more

accurate adjustment and comparison of interhospital AbC. Finally, further work on developing and validating antimicrobial use measures seems warranted.

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Appendix

Table A1 A List of the 52 Antibacterial Agents that Were Used to Calculate Antibacterial Consumption

Antibacterial Drug Class	Antibacterial Agents
β -lactamase-sensitive penicillins	amoxicillin, ampicillin, penicillin g potasium, penicillin g sodium, penicillin v potasium, piperacillin
β-lactam/β-lactamase inhibitor combinations	amoxicillin/clavulanate potassium, ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/calvulanate
Antistaphylococcal penicillins	dicloxacillin, nafcillin sodium, oxacillin sodium
First generation cephalosporins	cefazolin, cephalexin
Second generation cephalosporins	cefaclor, cefotetan, cefoxitin, cefuroxime
Third and fourth generation cephalosporins/Monobactam	cefepime, cefotaxime sodium, cefpodoxime, ceftazidime, ceftriaxone sodium, aztreonam
Carbapenems	doripenem, ertapenem sodium, imipenem/cilastatin, meropenem
Fluoroquinolones	ciprofloxacin, levofloxacin, moxifloxacin hydrochloride, norfloxacin
Aminoglycosides	amikacin, gentamicin sulfate, tobramycin
Macrolides	azithromycin, clarithromycin, erythromycin
Tetracyclines	demeclocycline, doxycycline, minocycline, tetracycline
Glycopeptides	vancomycin
Other anti-gram-positive agents	daptomycin, linezolid, tigecycline
Imidazoles	metronidazole
Sulfonamides	trimethoprim/sulfamethoxazole
Lincosamides	clindamycin
Miscellaneous	nitrofurantoin, sulfadiazine

Table A2 A List of the International Classification of Diseases, Ninth Revision (ICD-9-CM) Diagnosis and Procedure Codes that Compose the Different Diagnoses and Procedures

Diagnosis/Procedure	Diagnosis or Procedure Codes
Urinary tract infections	590.1x, 590.2, 590.3, 590.8x, 595.0, 599.0
Pneumonia	481, 482.x, 483.x, 484.x, 485, 486
Other infections	All codes from 001.0 to 041.9
Transplants	33.50, 33.52, 33.6, 37.51, 41.94, 46.97, 50.51, 50.59, 52.80, 55.69

Table A3 The Medicare Severity Diagnosis Related Groups (MS-DRGs) Composition of the 35 Clinical Service Lines

Abbreviations: BMT = Bone marrow transplant, CC = complications and comorbidities, MCC = major complications and comorbidities, MV = Mechanical ventilation, PDX = principal diagnosis, O.R. = operating room procedure, AMI = Acute myocardial infarction, HF = Heart failure

CSL Number	Clinical Service Line Name	MS-DRG Number	MS-DRG Clinical Condition
1	BMT	9	Bone marrow transplant (-FY2010)
1	BMT	14	Allogeneic Bone Marrow Transplant (FY2011+)
1	BMT	15	Autologous Bone Marrow Transplant (FY2011+)
2	Burns	927	Extensive burns or full thickness burns w MV 96+ hrs w skin graft
2	Burns	928	Full thickness burn w skin graft or inhal inj w CC/MCC
2	Burns	929	Full thickness burn w skin graft or inhal inj w/o CC/MCC
2	Burns	933	Extensive burns or full thickness burns w MV 96+ hrs w/o skin graft
2	Burns	934	Full thickness burn w/o skin grft or inhal inj
2	Burns	935	Non-extensive burns
3	Cardiology	222	Cardiac defib implant w cardiac cath w AMI/HF/shock w MCC
3	Cardiology	223	Cardiac defib implant w cardiac cath w AMI/HF/shock w/o MCC
3	Cardiology	224	Cardiac defib implant w cardiac cath w/o AMI/HF/shock w MCC
3	Cardiology	225	Cardiac defib implant w cardiac cath w/o AMI/HF/shock w/o MCC
3	Cardiology	226	Cardiac defibrillator implant w/o cardiac cath w MCC
3	Cardiology	227	Cardiac defibrillator implant w/o cardiac cath w/o MCC
3	Cardiology	242	Permanent cardiac pacemaker implant w MCC
3	Cardiology	243	Permanent cardiac pacemaker implant w CC
3	Cardiology	244	Permanent cardiac pacemaker implant w/o CC/MCC
3	Cardiology	245	AICD generator procedures (FY2009+)
3	Cardiology	246	Perc cardiovasc proc w drug-eluting stent w MCC or 4+ vessels/stents
3	Cardiology	247	Perc cardiovasc proc w drug-eluting stent w/o MCC
3	Cardiology	248	Perc cardiovasc proc w non-drug-eluting stent w MCC or 4+ ves/stents
3	Cardiology	249	Perc cardiovasc proc w non-drug-eluting stent w/o MCC
3	Cardiology	250	Perc cardiovasc proc w/o coronary artery stent or AMI w MCC

3	Cardiology	251	Perc cardiovasc proc w/o coronary artery stent or AMI w/o MCC
3	Cardiology	258	Cardiac pacemaker device replacement w MCC
3	Cardiology	259	Cardiac pacemaker device replacement w/o MCC
3	Cardiology	260	Cardiac pacemaker revision except device replacement w MCC
3	Cardiology	261	Cardiac pacemaker revision except device replacement w CC
3	Cardiology	262	Cardiac pacemaker revision except device replacement w/o CC/MCC
3	Cardiology	265	AICD lead procedures
3	Cardiology	280	Acute myocardial infarction, discharged alive w MCC
3	Cardiology	281	Acute myocardial infarction, discharged alive w CC
3	Cardiology	282	Acute myocardial infarction, discharged alive w/o CC/MCC
3	Cardiology	283	Acute myocardial infarction, expired w MCC
3	Cardiology	284	Acute myocardial infarction, expired w CC
3	Cardiology	285	Acute myocardial infarction, expired w/o CC/MCC
3	Cardiology	286	Circulatory disorders except AMI, w card cath w MCC
3	Cardiology	287	Circulatory disorders except AMI, w card cath w/o MCC
3	Cardiology	288	Acute & subacute endocarditis w MCC
3	Cardiology	289	Acute & subacute endocarditis w CC
3	Cardiology	290	Acute & subacute endocarditis w/o CC/MCC
3	Cardiology	291	Heart failure & shock w MCC
3	Cardiology	292	Heart failure & shock w CC
3	Cardiology	293	Heart failure & shock w/o CC/MCC
3	Cardiology	296	Cardiac arrest, unexplained w MCC
3	Cardiology	297	Cardiac arrest, unexplained w CC
3	Cardiology	298	Cardiac arrest, unexplained w/o CC/MCC
3	Cardiology	302	Atherosclerosis w MCC
3	Cardiology	303	Atherosclerosis w/o MCC
3	Cardiology	306	Cardiac congenital & valvular disorders w MCC
3	Cardiology	307	Cardiac congenital & valvular disorders w/o MCC
3	Cardiology	308	Cardiac arrhythmia & conduction disorders w MCC
3	Cardiology	309	Cardiac arrhythmia & conduction disorders w CC
3	Cardiology	310	Cardiac arrhythmia & conduction disorders w/o CC/MCC
3	Cardiology	311	Angina pectoris
3	Cardiology	314	Other circulatory system diagnoses w MCC
3	Cardiology	315	Other circulatory system diagnoses w CC
3	Cardiology	316	Other circulatory system diagnoses w/o CC/MCC
4	Cardiothoracic Surg	163	Major chest procedures w MCC
4	Cardiothoracic Surg	164	Major chest procedures w CC
4	Cardiothoracic Surg	165	Major chest procedures w/o CC/MCC
4	Cardiothoracic Surg	166	Other resp system O.R. procedures w MCC
4	Cardiothoracic Surg	167	Other resp system O.R. procedures w CC
4	Cardiothoracic Surg	168	Other resp system O.R. procedures w/o CC/MCC
4	Cardiothoracic Surg	216	Cardiac valve & oth maj cardiothoracic proc w card cath w MCC
4	Cardiothoracic Surg	217	Cardiac valve & oth maj cardiothoracic proc w card cath w CC
4	Cardiothoracic Surg	218	Cardiac valve & oth maj cardiothoracic proc w card cath w/o CC/MCC
4	Cardiothoracic Surg	219	Cardiac valve & oth maj cardiothoracic proc w/o card cath w MCC
4	Cardiothoracic Surg	220	Cardiac valve & oth maj cardiothoracic proc w/o card cath w CC
4	Cardiothoracic Surg	221	Cardiac valve & oth maj cardiothoracic proc w/o card cath w/o CC/MCC
4	Cardiothoracic Surg	228	Other cardiothoracic procedures w MCC
4	Cardiothoracic Surg	229	Other cardiothoracic procedures w CC
4	Cardiothoracic Surg	230	Other cardiothoracic procedures w/o CC/MCC
4	Cardiothoracic Surg	231	Coronary bypass w PTCA w MCC
4	Cardiothoracic Surg	232	Coronary bypass w PTCA w/o MCC
4	Cardiothoracic Surg	233	Coronary bypass w cardiac cath w MCC
4	Cardiothoracic Surg	234	Coronary bypass w cardiac cath w/o MCC
4	Cardiothoracic Surg	235	Coronary bypass w/o cardiac cath w MCC
4	Cardiothoracic Surg	236	Coronary bypass w/o cardiac cath w/o MCC
4	Cardiothoracic Surg	237	Major cardiovasc procedures w MCC or thoracic aortic anuerysm repair
4	Cardiothoracic Surg	238	Major cardiovascular procedures w/o MCC
5	Dental/Oral Surgery	137	Mouth procedures w CC/MCC
5	Dental/Oral Surgery	138	Mouth procedures w/o CC/MCC
5	Dental/Oral Surgery	157	Dental & Oral Diseases w MCC
5	Dental/Oral Surgery	158	Dental & Oral Diseases w CC
5	Dental/Oral Surgery	159	Dental & Oral Diseases w/o CC/MCC
6	Dermatology	595	Major skin disorders w MCC
6	Dermatology	596	Major skin disorders w/o MCC
6	Dermatology	606	Minor skin disorders w MCC
6	Dermatology	607	Minor skin disorders w/o MCC

7	Gastroenterology	368	Major esophageal disorders w MCC
7	Gastroenterology	369	Major esophageal disorders w CC
7	Gastroenterology	370	Major esophageal disorders w/o CC/MCC
7	Gastroenterology	371	Major gastrointestinal disorders & peritoneal infections w MCC
7	Gastroenterology	372	Major gastrointestinal disorders & peritoneal infections w CC
7	Gastroenterology	373	Major gastrointestinal disorders & peritoneal infections w/o CC/MCC
7	Gastroenterology	377	G.I. hemorrhage w MCC
7	Gastroenterology	378	G.I. hemorrhage w CC
7	Gastroenterology	379	G.I. hemorrhage w/o CC/MCC
7	Gastroenterology	380	Complicated peptic ulcer w MCC
7	Gastroenterology	381	Complicated peptic ulcer w CC
7	Gastroenterology	382	Complicated peptic ulcer w/o CC/MCC
7	Gastroenterology	385	Inflammatory bowel disease w MCC
7	Gastroenterology	386	Inflammatory bowel disease w CC
7	Gastroenterology	387	Inflammatory bowel disease w/o CC/MCC
7	Gastroenterology	388	G.I. obstruction w MCC
7	Gastroenterology	389	G.I. obstruction w CC
7	Gastroenterology	390	G.I. obstruction w/o CC/MCC
7	Gastroenterology	391	Esophagitis, gastroent & misc digest disorders w MCC
7	Gastroenterology	392	Esophagitis, gastroent & misc digest disorders w/o MCC
7	Gastroenterology	393	Other digestive system diagnoses w MCC
7	Gastroenterology	394	Other digestive system diagnoses w CC
7	Gastroenterology	395	Other digestive system diagnoses w/o CC/MCC
7	Gastroenterology	432	Cirrhosis & alcoholic hepatitis w MCC
7	Gastroenterology	433	Cirrhosis & alcoholic hepatitis w CC
7	Gastroenterology	434	Cirrhosis & alcoholic hepatitis w/o CC/MCC
7	Gastroenterology	438	Disorders of pancreas except malignancy w MCC
7	Gastroenterology	439	Disorders of pancreas except malignancy w CC
7	Gastroenterology	440	Disorders of pancreas except malignancy w/o CC/MCC
7	Gastroenterology	441	Disorders of liver except malig,cirr,alc hepa w MCC
7	Gastroenterology	442	Disorders of liver except malig,cirr,alc hepa w CC
7	Gastroenterology	443	Disorders of liver except malig,cirr,alc hepa w/o CC/MCC
7	Gastroenterology	444	Disorders of the biliary tract w MCC
7	Gastroenterology	445	Disorders of the biliary tract w CC
7	Gastroenterology	446	Disorders of the biliary tract w/o CC/MCC
8	Gynecology	742	Uterine & adnexa proc for non-malignancy w CC/MCC
8	Gynecology	743	Uterine & adnexa proc for non-malignancy w/o CC/MCC
8	Gynecology	744	D&C, conization, laparoscopy & tubal interruption w CC/MCC
8	Gynecology	745	D&C, conization, laparoscopy & tubal interruption w/o CC/MCC
8	Gynecology	746	Vagina, cervix & vulva procedures w CC/MCC
8	Gynecology	747	Vagina, cervix & vulva procedures w/o CC/MCC
8	Gynecology	748	Female reproductive system reconstructive procedures
8	Gynecology	749	Other female reproductive system O.R. procedures w CC/MCC
8	Gynecology	750	Other female reproductive system O.R. procedures w/o CC/MCC
8	Gynecology	757	Infections, female reproductive system w MCC
8	Gynecology	758	Infections, female reproductive system w CC
8	Gynecology	759	Infections, female reproductive system w/o CC/MCC
8	Gynecology	760	Menstrual & other female reproductive system disorders w CC/MCC
8	Gynecology	761	Menstrual & other female reproductive system disorders w/o CC/MCC
9	Heart Transplant or Implant of Heart Assist System	1	Heart transplant or implant of heart assist system w MCC
9	Heart Transplant or Implant of Heart Assist System	2	Heart transplant or implant of heart assist system w/o MCC
9	Heart Transplant or Implant of Heart Assist System	215	Other heart assist system implant
10	HIV	969	HIV w extensive O.R. procedure w MCC
10	HIV	970	HIV w extensive O.R. procedure w/o MCC
10	HIV	974	HIV w major related condition w MCC
10	HIV	975	HIV w major related condition w CC
10	HIV	976	HIV w major related condition w/o CC/MCC
10	HIV	977	HIV w or w/o other related condition
11	Kidney/Pancreas Transplant	8	Simultaneous pancreas/kidney transplant
11	Kidney/Pancreas Transplant	10	Pancreas transplant
11	Kidney/Pancreas Transplant	652	Kidney transplant
12	Liver Transplant	5	Liver transplant w MCC or intestinal transplant
12	Liver Transplant	6	Liver transplant w/o MCC
13	Lung Transplant	7	Lung transplant
14	Med Oncology	54	Nervous system neoplasms w MCC
14	Med Oncology	55	Nervous system neoplasms w/o MCC
14	Med Oncology	180	Respiratory neoplasms w MCC

14	Med Oncology	181	Respiratory neoplasms w CC
14	Med Oncology	182	Respiratory neoplasms w/o CC/MCC
14	Med Oncology	374	Digestive malignancy w MCC
14	Med Oncology	375	Digestive malignancy w CC
14	Med Oncology	376	Digestive malignancy w/o CC/MCC
14	Med Oncology	435	Malignancy of hepatobiliary system or pancreas w MCC
14	Med Oncology	436	Malignancy of hepatobiliary system or pancreas w CC
14	Med Oncology	437	Malignancy of hepatobiliary system or pancreas w/o CC/MCC
14	Med Oncology	542	Pathological fractures & musculoskelet & conn tiss malig w MCC
14	Med Oncology	543	Pathological fractures & musculoskelet & conn tiss malig w CC
14	Med Oncology	544	Pathological fractures & musculoskelet & conn tiss malig w/o CC/MCC
14	Med Oncology	597	Malignant breast disorders w MCC
14	Med Oncology	598	Malignant breast disorders w CC
14	Med Oncology	599	Malignant breast disorders w/o CC/MCC
14	Med Oncology	686	Kidney & urinary tract neoplasms w MCC
14	Med Oncology	687	Kidney & urinary tract neoplasms w CC
14	Med Oncology	688	Kidney & urinary tract neoplasms w/o CC/MCC
14	Med Oncology	834	Acute leukemia w/o major O.R. procedure w MCC
14	Med Oncology	835	Acute leukemia w/o major O.R. procedure w CC
14	Med Oncology	836	Acute leukemia w/o major O.R. procedure w/o CC/MCC
14	Med Oncology	837	Chemo w acute leukemia as sdx or w high dose chemo agent w MCC
14	Med Oncology	838	Chemo w acute leukemia as sdx w CC or high dose chemo agent
14	Med Oncology	839	Chemo w acute leukemia as sdx w/o CC/MCC
14	Med Oncology	840	Lymphoma & non-acute leukemia w MCC
14	Med Oncology	841	Lymphoma & non-acute leukemia w CC
14	Med Oncology	842	Lymphoma & non-acute leukemia w/o CC/MCC
14	Med Oncology	843	Other myeloprolif dis or poorly diff neopl diag w MCC
14	Med Oncology	844	Other myeloprolif dis or poorly diff neopl diag w CC
14	Med Oncology	845	Other myeloprolif dis or poorly diff neopl diag w/o CC/MCC
14	Med Oncology	846	Chemotherapy w/o acute leukemia as secondary diagnosis w MCC
14	Med Oncology	847	Chemotherapy w/o acute leukemia as secondary diagnosis w CC
14	Med Oncology	848	Chemotherapy w/o acute leukemia as secondary diagnosis w/o CC/MCC
14	Med Oncology	849	Radiotherapy
15	Medicine General	75	Viral meningitis w CC/MCC
15	Medicine General	76	Viral meningitis w/o CC/MCC
15	Medicine General	77	Hypertensive encephalopathy w MCC
15	Medicine General	78	Hypertensive encephalopathy w CC
15	Medicine General	79	Hypertensive encephalopathy w/o CC/MCC
15	Medicine General	94	Bacterial & tuberculous infections of nervous system w MCC
15	Medicine General	95	Bacterial & tuberculous infections of nervous system w CC
15	Medicine General	96	Bacterial & tuberculous infections of nervous system w/o CC/MCC
15	Medicine General	97	Non-bacterial infect of nervous sys exc viral meningitis w MCC
15	Medicine General	98	Non-bacterial infect of nervous sys exc viral meningitis w CC
15	Medicine General	99	Non-bacterial infect of nervous sys exc viral meningitis w/o CC/MCC
15	Medicine General	152	Otitis media & URI w MCC
15	Medicine General	153	Otitis media & URI w/o MCC
15	Medicine General	175	Pulmonary embolism w MCC
15	Medicine General	176	Pulmonary embolism w/o MCC
15	Medicine General	177	Respiratory infections & inflammations w MCC
15	Medicine General	178	Respiratory infections & inflammations w CC
15	Medicine General	179	Respiratory infections & inflammations w/o CC/MCC
15	Medicine General	186	Pleural effusion w MCC
15	Medicine General	187	Pleural effusion w CC
15	Medicine General	188	Pleural effusion w/o CC/MCC
15	Medicine General	189	Pulmonary edema & respiratory failure
15	Medicine General	190	Chronic obstructive pulmonary disease w MCC
15	Medicine General	191	Chronic obstructive pulmonary disease w CC
15	Medicine General	192	Chronic obstructive pulmonary disease w/o CC/MCC
15	Medicine General	193	Simple pneumonia & pleurisy w MCC
15	Medicine General	194	Simple pneumonia & pleurisy w CC
15	Medicine General	195	Simple pneumonia & pleurisy w/o CC/MCC
15	Medicine General	196	Interstitial lung disease w MCC
15	Medicine General	197	Interstitial lung disease w CC
15	Medicine General	198	Interstitial lung disease w/o CC/MCC
15	Medicine General	199	Pneumothorax w MCC
15	Medicine General	200	Pneumothorax w CC
15	Medicine General	201	Pneumothorax w/o CC/MCC

15	Medicine General	202	Bronchitis & asthma w CC/MCC
15	Medicine General	203	Bronchitis & asthma w/o CC/MCC
15	Medicine General	204	Respiratory signs & symptoms
15	Medicine General	205	Other respiratory system diagnoses w MCC
15	Medicine General	206	Other respiratory system diagnoses w/o MCC
15	Medicine General	208	Respiratory system diagnosis w ventilator support <96 hours
15	Medicine General	294	Deep vein thrombophlebitis w CC/MCC
15	Medicine General	295	Deep vein thrombophlebitis w/o CC/MCC
15	Medicine General	299	Peripheral vascular disorders w MCC
15	Medicine General	300	Peripheral vascular disorders w CC
15	Medicine General	301	Peripheral vascular disorders w/o CC/MCC
15	Medicine General	304	Hypertension w MCC
15	Medicine General	305	Hypertension w/o MCC
15	Medicine General	312	Syncope & collapse
15	Medicine General	313	Chest pain
15	Medicine General	383	Uncomplicated peptic ulcer w MCC
15	Medicine General	384	Uncomplicated peptic ulcer w/o MCC
15	Medicine General	539	Osteomyelitis w MCC
15	Medicine General	540	Osteomyelitis w CC
15	Medicine General	541	Osteomyelitis w/o CC/MCC
15	Medicine General	551	Medical back problems w MCC
15	Medicine General	552	Medical back problems w/o MCC
15	Medicine General	592	Skin ulcers w MCC
15	Medicine General	593	Skin ulcers w CC
15	Medicine General	594	Skin ulcers w/o CC/MCC
15	Medicine General	600	Non-malignant breast disorders w CC/MCC
15	Medicine General	601	Non-malignant breast disorders w/o CC/MCC
15	Medicine General	602	Cellulitis w MCC
15	Medicine General	603	Cellulitis w/o MCC
15	Medicine General	604	Trauma to the skin, subcut tiss & breast w MCC
15	Medicine General	605	Trauma to the skin, subcut tiss & breast w/o MCC
15	Medicine General	637	Diabetes w MCC
15	Medicine General	638	Diabetes w CC
15	Medicine General	639	Diabetes w/o CC/MCC
15	Medicine General	640	Nutritional & misc metabolic disorders w MCC
15	Medicine General	641	Nutritional & misc metabolic disorders w/o MCC
15	Medicine General	642	Inborn errors of metabolism
15	Medicine General	643	Endocrine disorders w MCC
15	Medicine General	644	Endocrine disorders w CC
15	Medicine General	645	Endocrine disorders w/o CC/MCC
15	Medicine General	682	Renal failure w MCC
15	Medicine General	683	Renal failure w CC
15	Medicine General	684	Renal failure w/o CC/MCC
15	Medicine General	685	Admit for renal dialysis
15	Medicine General	689	Kidney & urinary tract infections w MCC
15	Medicine General	690	Kidney & urinary tract infections w/o MCC
15	Medicine General	698	Other kidney & urinary tract diagnoses w MCC
15	Medicine General	699	Other kidney & urinary tract diagnoses w CC
15	Medicine General	700	Other kidney & urinary tract diagnoses w/o CC/MCC
15	Medicine General	808	Major hematol/immun diag exc sickle cell crisis & coagul w MCC
15	Medicine General	809	Major hematol/immun diag exc sickle cell crisis & coagul w CC
15	Medicine General	810	Major hematol/immun diag exc sickle cell crisis & coagul w/o CC/MCC
15	Medicine General	811	Red blood cell disorders w MCC
15	Medicine General	812	Red blood cell disorders w/o MCC
15	Medicine General	813	Coagulation disorders
15	Medicine General	814	Reticuloendothelial & immunity disorders w MCC
15	Medicine General	815	Reticuloendothelial & immunity disorders w CC
15	Medicine General	816	Reticuloendothelial & immunity disorders w/o CC/MCC
15	Medicine General	862	Postoperative & post-traumatic infections w MCC
15	Medicine General	863	Postoperative & post-traumatic infections w/o MCC
15	Medicine General	864	Fever of unknown origin
15	Medicine General	865	Viral illness w MCC
15	Medicine General	866	Viral illness w/o MCC
15	Medicine General	867	Other infectious & parasitic diseases diagnoses w MCC
15	Medicine General	868	Other infectious & parasitic diseases diagnoses w CC
15	Medicine General	869	Other infectious & parasitic diseases diagnoses w/o CC/MCC
15	Medicine General	871	Septicemia or severe sepsis w/o MV 96+ hours w MCC (FY2009+)

15	Medicine General	872	Septicemia or severe sepsis w/o MV 96+ hours w/o MCC (FY2009+)
15	Medicine General	915	Allergic reactions w MCC
15	Medicine General	916	Allergic reactions w/o MCC
15	Medicine General	917	Poisoning & toxic effects of drugs w MCC
15	Medicine General	918	Poisoning & toxic effects of drugs w/o MCC
15	Medicine General	922	Other injury, poisoning & toxic effect diag w MCC
15	Medicine General	923	Other injury, poisoning & toxic effect diag w/o MCC
15	Medicine General	947	Signs & symptoms w MCC
15	Medicine General	948	Signs & symptoms w/o MCC
15	Medicine General	949	Aftercare w CC/MCC
15	Medicine General	950	Aftercare w/o CC/MCC
15	Medicine General	951	Other factors influencing health status
16	Neurology	52	Spinal disorders & injuries w CC/MCC
16	Neurology	53	Spinal disorders & injuries w/o CC/MCC
16	Neurology	56	Degenerative nervous system disorders w MCC
16	Neurology	57	Degenerative nervous system disorders w/o MCC
16	Neurology	58	Multiple sclerosis & cerebellar ataxia w MCC
16	Neurology	59	Multiple sclerosis & cerebellar ataxia w CC
16	Neurology	60	Multiple sclerosis & cerebellar ataxia w/o CC/MCC
16	Neurology	61	Acute ischemic stroke w use of thrombolytic agent w MCC
16	Neurology	62	Acute ischemic stroke w use of thrombolytic agent w CC
16	Neurology	63	Acute ischemic stroke w use of thrombolytic agent w/o CC/MCC
16	Neurology	64	Intracranial hemorrhage or cerebral infarction w MCC
16	Neurology	65	Intracranial hemorrhage or cerebral infarction w CC
16	Neurology	66	Intracranial hemorrhage or cerebral infarction w/o CC/MCC
16	Neurology	67	Nonspecific cva & precerebral occlusion w/o infarct w MCC
16	Neurology	68	Nonspecific cva & precerebral occlusion w/o infarct w/o MCC
16	Neurology	69	Transient ischemia
16	Neurology	70	Nonspecific cerebrovascular disorders w MCC
16	Neurology	71	Nonspecific cerebrovascular disorders w CC
16	Neurology	72	Nonspecific cerebrovascular disorders w/o CC/MCC
16	Neurology	73	Cranial & peripheral nerve disorders w MCC
16	Neurology	74	Cranial & peripheral nerve disorders w/o MCC
16	Neurology	80	Nontraumatic stupor & coma w MCC
16	Neurology	81	Nontraumatic stupor & coma w/o MCC
16	Neurology	82	Traumatic stupor & coma, coma >1 hr w MCC
16	Neurology	83	Traumatic stupor & coma, coma >1 hr w CC
16	Neurology	84	Traumatic stupor & coma, coma >1 hr w/o CC/MCC
16	Neurology	85	Traumatic stupor & coma, coma <1 hr w MCC
16	Neurology	86	Traumatic stupor & coma, coma <1 hr w CC
16	Neurology	87	Traumatic stupor & coma, coma <1 hr w/o CC/MCC
16	Neurology	88	Concussion w MCC
16	Neurology	89	Concussion w CC
16	Neurology	90	Concussion w/o CC/MCC
16	Neurology	91	Other disorders of nervous system w MCC
16	Neurology	92	Other disorders of nervous system w CC
16	Neurology	93	Other disorders of nervous system w/o CC/MCC
16	Neurology	100	Seizures w MCC
16	Neurology	101	Seizures w/o MCC
16	Neurology	102	Headaches w MCC
16	Neurology	103	Headaches w/o MCC
16	Neurology	123	Neurological eye disorders
16	Neurology	149	Dysequilibrium
17	Neurosurgery	20	Intracranial vascular procedures w PDX hemorrhage w MCC
17	Neurosurgery	21	Intracranial vascular procedures w PDX hemorrhage w CC
17	Neurosurgery	22	Intracranial vascular procedures w PDX hemorrhage w/o CC/MCC
17	Neurosurgery	23	Cranio w major dev impl/acute complex CNS PDX w MCC or chemo implant
17	Neurosurgery	24	Cranio w major dev impl/acute complex CNS PDX w/o MCC
17	Neurosurgery	25	Craniotomy & endovascular intracranial procedures w MCC
17	Neurosurgery	26	Craniotomy & endovascular intracranial procedures w CC
17	Neurosurgery	27	Craniotomy & endovascular intracranial procedures w/o CC/MCC
17	Neurosurgery	31	Ventricular shunt procedures w MCC
17	Neurosurgery	32	Ventricular shunt procedures w CC
17	Neurosurgery	33	Ventricular shunt procedures w/o CC/MCC
17	Neurosurgery	40	Periph & cranial nerve & other nerv syst proc w MCC
17	Neurosurgery	41	Periph/cranial nerve & other nerv syst proc w CC or periph neurostim
17	Neurosurgery	42	Periph & cranial nerve & other nerv syst proc w/o CC/MCC

18	Obstetrics	765	Cesarean section w CC/MCC
18	Obstetrics	766	Cesarean section w/o CC/MCC
18	Obstetrics	767	Vaginal delivery w sterilization &/or D&C
18	Obstetrics	768	Vaginal delivery w O.R. proc except steril &/or D&C
18	Obstetrics	769	Postpartum & post abortion diagnoses w O.R. procedure
18	Obstetrics	770	Abortion w D&C, aspiration curettage or hysterotomy
18	Obstetrics	774	Vaginal delivery w complicating diagnoses
18	Obstetrics	775	Vaginal delivery w/o complicating diagnoses
18	Obstetrics	776	Postpartum & post abortion diagnoses w/o O.R. procedure
18	Obstetrics	777	Ectopic pregnancy
18	Obstetrics	778	Threatened abortion
18	Obstetrics	779	Abortion w/o D&C
18	Obstetrics	780	False labor
18	Obstetrics	781	Other antepartum diagnoses w medical complications
18	Obstetrics	782	Other antepartum diagnoses w/o medical complications
19	Ophthalmology	113	Orbital procedures w CC/MCC
19	Ophthalmology	114	Orbital procedures w/o CC/MCC
19	Ophthalmology	115	Extraocular procedures except orbit
19	Ophthalmology	116	Intraocular procedures w CC/MCC
19	Ophthalmology	117	Intraocular procedures w/o CC/MCC
19	Ophthalmology	121	Acute major eye infections w CC/MCC
19	Ophthalmology	122	Acute major eye infections w/o CC/MCC
19	Ophthalmology	124	Other disorders of the eye w MCC
19	Ophthalmology	125	Other disorders of the eye w/o MCC
20	Orthopedics	461	Bilateral or multiple major joint procs of lower extremity w MCC
20	Orthopedics	462	Bilateral or multiple major joint procs of lower extremity w/o MCC
20	Orthopedics	466	Revision of hip or knee replacement w MCC
20	Orthopedics	467	Revision of hip or knee replacement w CC
20	Orthopedics	468	Revision of hip or knee replacement w/o CC/MCC
20	Orthopedics	469	Major joint replacement or reattachment of lower extremity w MCC
20	Orthopedics	470	Major joint replacement or reattachment of lower extremity w/o MCC
20	Orthopedics	474	Amputation for musculoskeletal sys & conn tissue dis w MCC
20	Orthopedics	475	Amputation for musculoskeletal sys & conn tissue dis w CC
20	Orthopedics	476	Amputation for musculoskeletal sys & conn tissue dis w/o CC/MCC
20	Orthopedics	477	Biopsies of musculoskeletal system & connective tissue w MCC
20	Orthopedics	478	Biopsies of musculoskeletal system & connective tissue w CC
20	Orthopedics	479	Biopsies of musculoskeletal system & connective tissue w/o CC/MCC
20	Orthopedics	480	Hip & femur procedures except major joint w MCC
20	Orthopedics	481	Hip & femur procedures except major joint w CC
20	Orthopedics	482	Hip & femur procedures except major joint w/o CC/MCC
20	Orthopedics	483	Major joint & limb reattachment proc of upper extremity w CC/MCC
20	Orthopedics	484	Major joint & limb reattachment proc of upper extremity w/o CC/MCC
20	Orthopedics	485	Knee procedures w pdx of infection w MCC
20	Orthopedics	486	Knee procedures w pdx of infection w CC
20	Orthopedics	487	Knee procedures w pdx of infection w/o CC/MCC
20	Orthopedics	488	Knee procedures w/o pdx of infection w CC/MCC
20	Orthopedics	489	Knee procedures w/o pdx of infection w/o CC/MCC
20	Orthopedics	492	Lower extrem & humer proc except hip,foot,femur w MCC
20	Orthopedics	493	Lower extrem & humer proc except hip,foot,femur w CC
20	Orthopedics	494	Lower extrem & humer proc except hip,foot,femur w/o CC/MCC
20	Orthopedics	495	Local excision & removal int fix devices exc hip & femur w MCC
20	Orthopedics	496	Local excision & removal int fix devices exc hip & femur w CC
20	Orthopedics	497	Local excision & removal int fix devices exc hip & femur w/o CC/MCC
20	Orthopedics	498	Local excision & removal int fix devices of hip & femur w CC/MCC
20	Orthopedics	499	Local excision & removal int fix devices of hip & femur w/o CC/MCC
20	Orthopedics	500	Soft tissue procedures w MCC
20	Orthopedics	501	Soft tissue procedures w CC
20	Orthopedics	502	Soft tissue procedures w/o CC/MCC
20	Orthopedics	503	Foot procedures w MCC
20	Orthopedics	504	Foot procedures w CC
20	Orthopedics	505	Foot procedures w/o CC/MCC
20	Orthopedics	506	Major thumb or joint procedures
20	Orthopedics	507	Major shoulder or elbow joint procedures w CC/MCC
20	Orthopedics	508	Major shoulder or elbow joint procedures w/o CC/MCC
20	Orthopedics	509	Arthroscopy
20	Orthopedics	510	Shoulder,elbow or forearm proc,exc major joint proc w MCC
20	Orthopedics	511	Shoulder,elbow or forearm proc,exc major joint proc w CC

20	Orthopedics	512	Shoulder,elbow or forearm proc,exc major joint proc w/o CC/MCC
20	Orthopedics	513	Hand or wrist proc, except major thumb or joint proc w CC/MCC
20	Orthopedics	514	Hand or wrist proc, except major thumb or joint proc w/o CC/MCC
20	Orthopedics	515	Other musculoskelet sys & conn tiss O.R. proc w MCC
20	Orthopedics	516	Other musculoskelet sys & conn tiss O.R. proc w CC
20	Orthopedics	517	Other musculoskelet sys & conn tiss O.R. proc w/o CC/MCC
20	Orthopedics	533	Fractures of femur w MCC
20	Orthopedics	534	Fractures of femur w/o MCC
20	Orthopedics	535	Fractures of hip & pelvis w MCC
20	Orthopedics	536	Fractures of hip & pelvis w/o MCC
20	Orthopedics	537	Sprains, strains, & dislocations of hip, pelvis & thigh w CC/MCC
20	Orthopedics	538	Sprains, strains, & dislocations of hip, pelvis & thigh w/o CC/MCC
20	Orthopedics	559	Aftercare, musculoskeletal system & connective tissue w MCC
20	Orthopedics	560	Aftercare, musculoskeletal system & connective tissue w CC
20	Orthopedics	561	Aftercare, musculoskeletal system & connective tissue w/o CC/MCC
20	Orthopedics	562	Fx, sprn, strn & disl except femur, hip, pelvis & thigh w MCC
20	Orthopedics	563	Fx, sprn, strn & disl except femur, hip, pelvis & thigh w/o MCC
20	Orthopedics	906	Hand procedures for injuries
21	Otolaryngology	11	Tracheostomy for face,mouth & neck diagnoses w MCC
21	Otolaryngology	12	Tracheostomy for face,mouth & neck diagnoses w CC
21	Otolaryngology	13	Tracheostomy for face,mouth & neck diagnoses w/o CC/MCC
21	Otolaryngology	129	Major head & neck procedures w CC/MCC or major device
21	Otolaryngology	130	Major head & neck procedures w/o CC/MCC
21	Otolaryngology	131	Cranial/facial procedures w CC/MCC
21	Otolaryngology	132	Cranial/facial procedures w/o CC/MCC
21	Otolaryngology	133	Other ear, nose, mouth & throat O.R. procedures w CC/MCC
21	Otolaryngology	134	Other ear, nose, mouth & throat O.R. procedures w/o CC/MCC
21	Otolaryngology	135	Sinus & mastoid procedures w CC/MCC
21	Otolaryngology	136	Sinus & mastoid procedures w/o CC/MCC
21	Otolaryngology	139	Salivary gland procedures
21	Otolaryngology	146	Ear, nose, mouth & throat malignancy w MCC
21	Otolaryngology	147	Ear, nose, mouth & throat malignancy w CC
21	Otolaryngology	148	Ear, nose, mouth & throat malignancy w/o CC/MCC
21	Otolaryngology	150	Epistaxis w MCC
21	Otolaryngology	151	Epistaxis w/o MCC
21	Otolaryngology	154	Nasal trauma & deformity w MCC
21	Otolaryngology	155	Nasal trauma & deformity w CC
21	Otolaryngology	156	Nasal trauma & deformity w/o CC/MCC
22	Plastic Surgery	463	Wnd debrid & skn grft exc hand, for musculo-conn tiss dis w MCC
22	Plastic Surgery	464	Wnd debrid & skn grft exc hand, for musculo-conn tiss dis w CC
22	Plastic Surgery	465	Wnd debrid & skn grft exc hand, for musculo-conn tiss dis w/o CC/MCC
22	Plastic Surgery	573	Skin graft &/or debrid for skn ulcer or cellulitis w MCC
22	Plastic Surgery	574	Skin graft &/or debrid for skn ulcer or cellulitis w CC
22	Plastic Surgery	575	Skin graft &/or debrid for skn ulcer or cellulitis w/o CC/MCC
22	Plastic Surgery	576	Skin graft &/or debrid exc for skin ulcer or cellulitis w MCC
22	Plastic Surgery	577	Skin graft &/or debrid exc for skin ulcer or cellulitis w CC
22	Plastic Surgery	578	Skin graft &/or debrid exc for skin ulcer or cellulitis w/o CC/MCC
22	Plastic Surgery	622	Skin grafts & wound debrid for endoc, nutrit & metab dis w MCC
22	Plastic Surgery	623	Skin grafts & wound debrid for endoc, nutrit & metab dis w CC
22	Plastic Surgery	624	Skin grafts & wound debrid for endoc, nutrit & metab dis w/o CC/MCC
22	Plastic Surgery	904	Skin grafts for injuries w CC/MCC
22	Plastic Surgery	905	Skin grafts for injuries w/o CC/MCC
23	Psychiatry	880	Acute adjustment reaction & psychosocial dysfunction
23	Psychiatry	881	Depressive neuroses
23	Psychiatry	882	Neuroses except depressive
23	Psychiatry	883	Disorders of personality & impulse control
23	Psychiatry	884	Organic disturbances & mental retardation
23	Psychiatry	885	Psychoses
23	Psychiatry	886	Behavioral & developmental disorders
23	Psychiatry	887	Other mental disorder diagnoses
24	Rehabilitation	945	Rehabilitation w CC/MCC
24	Rehabilitation	946	Rehabilitation w/o CC/MCC
25	Rheumatology	545	Connective tissue disorders w MCC
25	Rheumatology	546	Connective tissue disorders w CC
25	Rheumatology	547	Connective tissue disorders w/o CC/MCC
25	Rheumatology	548	Septic arthritis w MCC
25	Rheumatology	549	Septic arthritis w CC

25	Rheumatology	550	Septic arthritis w/o CC/MCC
25	Rheumatology	553	Bone diseases & arthropathies w MCC
25	Rheumatology	554	Bone diseases & arthropathies w/o MCC
25	Rheumatology	555	Signs & symptoms of musculoskeletal system & conn tissue w MCC
25	Rheumatology	556	Signs & symptoms of musculoskeletal system & conn tissue w/o MCC
25	Rheumatology	557	Tendonitis, myositis & bursitis w MCC
25	Rheumatology	558	Tendonitis, myositis & bursitis w/o MCC
25	Rheumatology	564	Other musculoskeletal sys & connective tissue diagnoses w MCC
25	Rheumatology	565	Other musculoskeletal sys & connective tissue diagnoses w CC
25	Rheumatology	566	Other musculoskeletal sys & connective tissue diagnoses w/o CC/MCC
26	Substance Abuse	894	Alcohol/drug abuse or dependence, left ama
26	Substance Abuse	895	Alcohol/drug abuse or dependence w rehabilitation therapy
26	Substance Abuse	896	Alcohol/drug abuse or dependence w/o rehabilitation therapy w MCC
26	Substance Abuse	897	Alcohol/drug abuse or dependence w/o rehabilitation therapy w/o MCC
27	Surg Oncology	582	Mastectomy for malignancy w CC/MCC
27	Surg Oncology	583	Mastectomy for malignancy w/o CC/MCC
27	Surg Oncology	820	Lymphoma & leukemia w major O.R. procedure w MCC
27	Surg Oncology	821	Lymphoma & leukemia w major O.R. procedure w CC
27	Surg Oncology	822	Lymphoma & leukemia w major O.R. procedure w/o CC/MCC
27	Surg Oncology	823	Lymphoma & non-acute leukemia w other O.R. proc w MCC
27	Surg Oncology	824	Lymphoma & non-acute leukemia w other O.R. proc w CC
27	Surg Oncology	825	Lymphoma & non-acute leukemia w other O.R. proc w/o CC/MCC
27	Surg Oncology	826	Myeloprolif disord or poorly diff neopl w maj O.R. proc w MCC
27	Surg Oncology	827	Myeloprolif disord or poorly diff neopl w maj O.R. proc w CC
27	Surg Oncology	828	Myeloprolif disord or poorly diff neopl w maj O.R. proc w/o CC/MCC
27	Surg Oncology	829	Myeloprolif disord or poorly diff neopl w other O.R. proc w CC/MCC
27	Surg Oncology	830	Myeloprolif disord or poorly diff neopl w other O.R. proc w/o CC/MCC
28	Surgery General	239	Amputation for circ sys disorders exc upper limb & toe w MCC
28	Surgery General	240	Amputation for circ sys disorders exc upper limb & toe w CC
28	Surgery General	241	Amputation for circ sys disorders exc upper limb & toe w/o CC/MCC
28	Surgery General	255	Upper limb & toe amputation for circ system disorders w MCC
28	Surgery General	256	Upper limb & toe amputation for circ system disorders w CC
28	Surgery General	257	Upper limb & toe amputation for circ system disorders w/o CC/MCC
28	Surgery General	264	Other circulatory system O.R. procedures
28	Surgery General	326	Stomach, esophageal & duodenal proc w MCC
28	Surgery General	327	Stomach, esophageal & duodenal proc w CC
28	Surgery General	328	Stomach, esophageal & duodenal proc w/o CC/MCC
28	Surgery General	329	Major small & large bowel procedures w MCC
28	Surgery General	330	Major small & large bowel procedures w CC
28	Surgery General	331	Major small & large bowel procedures w/o CC/MCC
28	Surgery General	332	Rectal resection w MCC
28	Surgery General	333	Rectal resection w CC
28	Surgery General	334	Rectal resection w/o CC/MCC
28	Surgery General	335	Peritoneal adhesiolysis w MCC
28	Surgery General	336	Peritoneal adhesiolysis w CC
28	Surgery General	337	Peritoneal adhesiolysis w/o CC/MCC
28	Surgery General	338	Appendectomy w complicated principal diag w MCC
28	Surgery General	339	Appendectomy w complicated principal diag w CC
28	Surgery General	340	Appendectomy w complicated principal diag w/o CC/MCC
28	Surgery General	341	Appendectomy w/o complicated principal diag w MCC
28	Surgery General	342	Appendectomy w/o complicated principal diag w CC
28	Surgery General	343	Appendectomy w/o complicated principal diag w/o CC/MCC
28	Surgery General	344	Minor small & large bowel procedures w MCC
28	Surgery General	345	Minor small & large bowel procedures w CC
28	Surgery General	346	Minor small & large bowel procedures w/o CC/MCC
28	Surgery General	347	Anal & stomal procedures w MCC
28	Surgery General	348	Anal & stomal procedures w CC
28	Surgery General	349	Anal & stomal procedures w/o CC/MCC
28	Surgery General	350	Inguinal & femoral hernia procedures w MCC
28	Surgery General	351	Inguinal & femoral hernia procedures w CC
28	Surgery General	352	Inguinal & femoral hernia procedures w/o CC/MCC
28	Surgery General	353	Hernia procedures except inguinal & femoral w MCC
28	Surgery General	354	Hernia procedures except inguinal & femoral w CC
28	Surgery General	355	Hernia procedures except inguinal & femoral w/o CC/MCC
28	Surgery General	356	Other digestive system O.R. procedures w MCC
28	Surgery General	357	Other digestive system O.R. procedures w CC
28	Surgery General	358	Other digestive system O.R. procedures w/o CC/MCC

28	Surgery General	405	Pancreas, liver & shunt procedures w MCC
28	Surgery General	406	Pancreas, liver & shunt procedures w CC
28	Surgery General	407	Pancreas, liver & shunt procedures w/o CC/MCC
28	Surgery General	408	Biliary tract proc except only cholecyst w or w/o c.d.e. w MCC
28	Surgery General	409	Biliary tract proc except only cholecyst w or w/o c.d.e. w CC
28	Surgery General	410	Biliary tract proc except only cholecyst w or w/o c.d.e. w/o CC/MCC
28	Surgery General	411	Cholecystectomy w c.d.e. w MCC
28	Surgery General	412	Cholecystectomy w c.d.e. w CC
28	Surgery General	413	Cholecystectomy w c.d.e. w/o CC/MCC
28	Surgery General	414	Cholecystectomy except by laparoscope w/o c.d.e. w MCC
28	Surgery General	415	Cholecystectomy except by laparoscope w/o c.d.e. w CC
28	Surgery General	416	Cholecystectomy except by laparoscope w/o c.d.e. w/o CC/MCC
28	Surgery General	417	Laparoscopic cholecystectomy w/o c.d.e. w MCC
28	Surgery General	418	Laparoscopic cholecystectomy w/o c.d.e. w CC
28	Surgery General	419	Laparoscopic cholecystectomy w/o c.d.e. w/o CC/MCC
28	Surgery General	420	Hepatobiliary diagnostic procedures w MCC
28	Surgery General	421	Hepatobiliary diagnostic procedures w CC
28	Surgery General	422	Hepatobiliary diagnostic procedures w/o CC/MCC
28	Surgery General	423	Other hepatobiliary or pancreas O.R. procedures w MCC
28	Surgery General	424	Other hepatobiliary or pancreas O.R. procedures w CC
28	Surgery General	425	Other hepatobiliary or pancreas O.R. procedures w/o CC/MCC
28	Surgery General	579	Other skin, subcut tiss & breast proc w MCC
28	Surgery General	580	Other skin, subcut tiss & breast proc w CC
28	Surgery General	581	Other skin, subcut tiss & breast proc w/o CC/MCC
28	Surgery General	584	Breast biopsy, local excision & other breast procedures w CC/MCC
28	Surgery General	585	Breast biopsy, local excision & other breast procedures w/o CC/MCC
28	Surgery General	614	Adrenal & pituitary procedures w CC/MCC
28	Surgery General	615	Adrenal & pituitary procedures w/o CC/MCC
28	Surgery General	616	Amputat of lower limb for endocrine,nutrit,& metabol dis w MCC
28	Surgery General	617	Amputat of lower limb for endocrine,nutrit,& metabol dis w CC
28	Surgery General	618	Amputat of lower limb for endocrine,nutrit,& metabol dis w/o CC/MCC
28	Surgery General	619	O.R. procedures for obesity w MCC
28	Surgery General	620	O.R. procedures for obesity w CC
28	Surgery General	621	O.R. procedures for obesity w/o CC/MCC
28	Surgery General	625	Thyroid, parathyroid & thyroglossal procedures w MCC
28	Surgery General	626	Thyroid, parathyroid & thyroglossal procedures w CC
28	Surgery General	627	Thyroid, parathyroid & thyroglossal procedures w/o CC/MCC
28	Surgery General	628	Other endocrine, nutrit & metab O.R. proc w MCC
28	Surgery General	629	Other endocrine, nutrit & metab O.R. proc w CC
28	Surgery General	630	Other endocrine, nutrit & metab O.R. proc w/o CC/MCC
28	Surgery General	799	Splenectomy w MCC
28	Surgery General	800	Splenectomy w CC
28	Surgery General	801	Splenectomy w/o CC/MCC
28	Surgery General	802	Other O.R. proc of the blood & blood forming organs w MCC
28	Surgery General	803	Other O.R. proc of the blood & blood forming organs w CC
28	Surgery General	804	Other O.R. proc of the blood & blood forming organs w/o CC/MCC
28	Surgery General	853	Infectious & parasitic diseases w O.R. procedure w MCC
28	Surgery General	854	Infectious & parasitic diseases w O.R. procedure w CC
28	Surgery General	855	Infectious & parasitic diseases w O.R. procedure w/o CC/MCC
28	Surgery General	856	Postoperative or post-traumatic infections w O.R. proc w MCC
28	Surgery General	857	Postoperative or post-traumatic infections w O.R. proc w CC
28	Surgery General	858	Postoperative or post-traumatic infections w O.R. proc w/o CC/MCC
28	Surgery General	876	O.R. procedure w principal diagnoses of mental illness
28	Surgery General	901	Wound debridements for injuries w MCC
28	Surgery General	902	Wound debridements for injuries w CC
28	Surgery General	903	Wound debridements for injuries w/o CC/MCC
28	Surgery General	939	O.R. proc w diagnoses of other contact w health services w MCC
28	Surgery General	940	O.R. proc w diagnoses of other contact w health services w CC
28	Surgery General	941	O.R. proc w diagnoses of other contact w health services w/o CC/MCC
28	Surgery General	981	Extensive O.R. procedure unrelated to principal diagnosis w MCC
28	Surgery General	982	Extensive O.R. procedure unrelated to principal diagnosis w CC
28	Surgery General	983	Extensive O.R. procedure unrelated to principal diagnosis w/o CC/MCC
28	Surgery General	987	Non-extensive O.R. proc unrelated to principal diagnosis w MCC
28	Surgery General	988	Non-extensive O.R. proc unrelated to principal diagnosis w CC
28	Surgery General	989	Non-extensive O.R. proc unrelated to principal diagnosis w/o CC/MCC
29	Trauma	183	Major chest trauma w MCC
29	Trauma	184	Major chest trauma w CC

29	Trauma	185	Major chest trauma w/o CC/MCC
29	Trauma	913	Traumatic injury w MCC
29	Trauma	914	Traumatic injury w/o MCC
29	Trauma	955	Craniotomy for multiple significant trauma
29	Trauma	956	Limb reattachment, hip & femur proc for multiple significant trauma
29	Trauma	957	Other O.R. procedures for multiple significant trauma w MCC
29	Trauma	958	Other O.R. procedures for multiple significant trauma w CC
29	Trauma	959	Other O.R. procedures for multiple significant trauma w/o CC/MCC
29	Trauma	963	Other multiple significant trauma w MCC
29	Trauma	964	Other multiple significant trauma w CC
29	Trauma	965	Other multiple significant trauma w/o CC/MCC
30	Urology	653	Major bladder procedures w MCC
30	Urology	654	Major bladder procedures w CC
30	Urology	655	Major bladder procedures w/o CC/MCC
30	Urology	656	Kidney & ureter procedures for neoplasm w MCC
30	Urology	657	Kidney & ureter procedures forneoplasm w CC
30	Urology	658	Kidney & ureter procedures for neoplasm w/o CC/MCC
30	Urology	659	Kidney & ureter procedures for non-neoplasm w MCC
30	Urology	660	Kidney & ureter procedures for non-neoplasm w CC
30	Urology	661	Kidney & ureter procedures for non-neoplasm w/o CC/MCC
30	Urology	662	Minor bladder procedures w MCC
30	Urology	663	Minor bladder procedures w CC
30	Urology	664	Minor bladder procedures w/o CC/MCC
30	Urology	665	Prostatectomy w MCC
30	Urology	666	Prostatectomy w CC
30	Urology	667	Prostatectomy w/o CC/MCC
30	Urology	668	Transurethral procedures w MCC
30	Urology	669	Transurethral procedures w CC
30	Urology	670	Transurethral procedures w/o CC/MCC
30	Urology	671	Urethral procedures w CC/MCC
30	Urology	672	Urethral procedures w/o CC/MCC
30	Urology	673	Other kidney & urinary tract procedures w MCC
30	Urology	674	Other kidney & urinary tract procedures w CC
30	Urology	675	Other kidney & urinary tract procedures w/o CC/MCC
30	Urology	691	Urinary stones w esw lithotripsy w CC/MCC
30	Urology	692	Urinary stones w esw lithotripsy w/o CC/MCC
30	Urology	693	Urinary stones w/o esw lithotripsy w MCC
30	Urology	694	Urinary stones w/o esw lithotripsy w/o MCC
30	Urology	695	Kidney & urinary tract signs & symptoms w MCC
30	Urology	696	Kidney & urinary tract signs & symptoms w/o MCC
30	Urology	697	Urethral stricture
30	Urology	707	Major male pelvic procedures w CC/MCC
30	Urology	708	Major male pelvic procedures w/o CC/MCC
30	Urology	709	Penis procedures w CC/MCC
30	Urology	710	Penis procedures w/o CC/MCC
30	Urology	711	Testes procedures w CC/MCC
30	Urology	712	Testes procedures w/o CC/MCC
30	Urology	713	Transurethral prostatectomy w CC/MCC
30	Urology	714	Transurethral prostatectomy w/o CC/MCC
30	Urology	715	Other male reproductive system O.R. proc for malignancy w CC/MCC
30	Urology	716	Other male reproductive system O.R. proc for malignancy w/o CC/MCC
30	Urology	717	Other male reproductive system O.R. proc exc malignancy w CC/MCC
30	Urology	718	Other male reproductive system O.R. proc exc malignancy w/o CC/MCC
30	Urology	722	Malignancy, male reproductive system w MCC
30	Urology	723	Malignancy, male reproductive system w CC
30	Urology	724	Malignancy, male reproductive system w/o CC/MCC
30	Urology	725	Benign prostatic hypertrophy w MCC
30	Urology	726	Benign prostatic hypertrophy w/o MCC
30	Urology	727	Inflammation of the male reproductive system w MCC
30	Urology	728	Inflammation of the male reproductive system w/o MCC
30	Urology	729	Other male reproductive system diagnoses w CC/MCC
30	Urology	730	Other male reproductive system diagnoses w/o CC/MCC
30	Urology	984	Prostatic O.R. procedure unrelated to principal diagnosis w MCC
30	Urology	985	Prostatic O.R. procedure unrelated to principal diagnosis w CC
30	Urology	986	Prostatic O.R. procedure unrelated to principal diagnosis w/o CC/MCC
31	Vascular Surgery	34	Carotid artery stent procedure w MCC
31	Vascular Surgery	35	Carotid artery stent procedure w CC

31	Vascular Surgery	36	Carotid artery stent procedure w/o CC/MCC
31	Vascular Surgery	37	Extracranial procedures w MCC
31	Vascular Surgery	38	Extracranial procedures w CC
31	Vascular Surgery	39	Extracranial procedures w/o CC/MCC
31	Vascular Surgery	252	Other vascular procedures w MCC
31	Vascular Surgery	253	Other vascular procedures w CC
31	Vascular Surgery	254	Other vascular procedures w/o CC/MCC
31	Vascular Surgery	263	Vein ligation & stripping
32	Ventilator Support	3	ECMO or trach w MV 96+ hrs or PDX exc face, mouth & neck w maj O.R.
32	Ventilator Support	4	Trach w MV 96+ hrs or PDX exc face, mouth & neck w/o maj O.R.
32	Ventilator Support	207	Respiratory system diagnosis w ventilator support 96+ hours
32	Ventilator Support	870	Septicemia or severe sepsis w MV 96+ hours (FY2009+)
33	Spinal Surgery	28	Spinal procedures w MCC
33	Spinal Surgery	29	Spinal procedures w CC or spinal neurostimulators
33	Spinal Surgery	30	Spinal procedures w/o CC/MCC
33	Spinal Surgery	453	Combined anterior/posterior spinal fusion w MCC
33	Spinal Surgery	454	Combined anterior/posterior spinal fusion w CC
33	Spinal Surgery	455	Combined anterior/posterior spinal fusion w/o CC/MCC
33	Spinal Surgery	456	Spinal fus exc cerv w spinal curv/malig/infec or 9+ fus w MCC
33	Spinal Surgery	457	Spinal fus exc cerv w spinal curv/malig/infec or 9+ fus w CC
33	Spinal Surgery	458	Spinal fus exc cerv w spinal curv/malig/infec or 9+ fus w/o CC/MCC
33	Spinal Surgery	459	Spinal fusion except cervical w MCC
33	Spinal Surgery	460	Spinal fusion except cervical w/o MCC
33	Spinal Surgery	471	Cervical spinal fusion w MCC
33	Spinal Surgery	472	Cervical spinal fusion w CC
33	Spinal Surgery	473	Cervical spinal fusion w/o CC/MCC
33	Spinal Surgery	490	Back & neck proc exc spinal fusion w CC/MCC or disc device/neurostim
33	Spinal Surgery	491	Back & neck proc exc spinal fusion w/o CC/MCC
34	Injuries/complications of prior care	907	Other O.R. procedures for injuries w MCC
34	Injuries/complications of prior care	908	Other O.R. procedures for injuries w CC
34	Injuries/complications of prior care	909	Other O.R. procedures for injuries w/o CC/MCC
34	Injuries/complications of prior care	919	Complications of treatment w MCC
34	Injuries/complications of prior care	920	Complications of treatment w CC
34	Injuries/complications of prior care	921	Complications of treatment w/o CC/MCC
35	Gynecology/Oncology	734	Pelvic evisceration, rad hysterectomy & rad vulvectomy w CC/MCC
35	Gynecology/Oncology	735	Pelvic evisceration, rad hysterectomy & rad vulvectomy w/o CC/MCC
35	Gynecology/Oncology	736	Uterine & adnexa proc for ovarian or adnexal malignancy w MCC
35	Gynecology/Oncology	737	Uterine & adnexa proc for ovarian or adnexal malignancy w CC
35	Gynecology/Oncology	738	Uterine & adnexa proc for ovarian or adnexal malignancy w/o CC/MCC
35	Gynecology/Oncology	739	Uterine,adnexa proc for non-ovarian/adnexal malig w MCC
35	Gynecology/Oncology	740	Uterine,adnexa proc for non-ovarian/adnexal malig w CC
35	Gynecology/Oncology	741	Uterine,adnexa proc for non-ovarian/adnexal malig w/o CC/MCC
35	Gynecology/Oncology	754	Malignancy, female reproductive system w MCC
35	Gynecology/Oncology	755	Malignancy, female reproductive system w CC
35	Gynecology/Oncology	756	Malignancy, female reproductive system w/o CC/MCC

Vita

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Date and Place of Birth Aug 17 1977 Amman, Jordan

Education

Ph.D.	Pharmacotherapy and Outcomes Science	August 2012 Virginia Commonwealth University Richmond, VA
B.Sc.	Pharmacy	June 2000 University of Jordan Amman, Jordan

Professional Experience

Teaching Assistant, Virginia Commonwealth University Aug 2007- May 2008
(Richmond, Virginia) Aug 2009- May 2010

Pharmacy Skills Lab (1 Semester)
Biostatistical Methods I & II (3 Semesters)

Hospital Pharmacist, King Hussein Cancer Center May 2004- July 2005
(Amman, Jordan)

Inpatient, outpatient and chemotherapy pharmacies

Chief Pharmacist, Malhas Hospital Sep 2002- April 2004
(Amman, Jordan)

Retail Pharmacist, Several Retail Pharmacies Aug 2000- Aug 2004
(Amman, Jordan)

Teaching Assistant (Instructor) Sep 2000- June 2002
School of Pharmacy, University of Jordan (Amman, Jordan)

Medicinal Chemistry Lab (2 Semesters)
Physical Pharmacy Lab (2 Semesters)

Relevant Graduate Course Work: GPA 4.00

Biostatistical Methods I and II	Epidemiology I and II
Applied Statistics I and II	Clinical Epidemiology
Applied Linear Regression	Pharmacoepidemiology
Advanced Regression	Clinical Trials
Multivariate Analysis	Biostatistical Computing
Analysis of Biomedical Data	Advanced Pharmacotherapy Research Methods

Computer Skills

SAS, JMP, Microsoft Office

Research Interests

Infectious Diseases, Design and Analysis of Pharmacoepidemiology Studies

Memberships

Jordan Pharmaceutical Association

Publications

Ibrahim OM, Polk RE. Benchmarking antimicrobial drug use in hospitals. *Expert Rev Anti Infect Ther.* 10(4):445-57 (2012).

Polk RE, Hohmann SF, Medvedev S, Ibrahim O. Benchmarking Risk-Adjusted Adult Antibacterial Drug Use in 70 US Academic Medical Center Hospitals. *Clinical Infectious Diseases.* 53(11), 1100-1110 (2011).

Pakyz AL, Gurgle HE, Ibrahim OM, Oinonen MJ, Polk RE. Trends in antibacterial use in pediatric patients in United States academic health centers. *Infect Control Hosp Epidemiol.* Jun;30(6):600-3 (2009).

Presentations at National Meetings

Development of a Risk-adjusted Model to Benchmark Antibacterial Drug Use in the University Health System Consortium Hospitals

Annual Infectious Diseases Pharmacotherapy Fellowship Forum Aspen, CO May 20-23 2010

Honors and Awards

Fulbright Student (Pre-doctoral) Scholarship	Aug 2005-July 2007
Phi Kappa Phi Honor Society, Academic Excellence Award (Masters)	2008