Evidence to Support Antibiotic Stewardship: Evaluating Current Strategies for Benchmarking Antibiotic Use in the Hospital Setting

By

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A DISSERTATION

Presented to the PhD in Epidemiology Program
School of Public Health
Oregon Health & Science University - Portland State University
in partial fulfillment of the requirements for the degree of:

Doctor of Philosophy

November 22, 2019

School of Public Health

Oregon Health & Science University — Portland State University

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DEDICATION

With thanks to my parents who encouraged me to dream,

and with hopes for the dreams that my children will have.

ACKNOWLEDGEMENTS

While my name may be printed on the title page of this document, I certainly did not complete this dissertation alone. I extend my deepest gratitude to my dissertation committee, specifically my chair, Dr. Jessina McGregor, who has filled many roles beyond committee chair. Jessina, you have been my mentor, advisor, and confidante through all phases of my PhD journey. I've admired your skills as an epidemiologist and mentor since the day we met. For your wisdom, persistent belief in my abilities, and profound generosity with your time, I am forever grateful. I am also indebted to the wise counsel and support of my other committee members: Drs. Rochelle Fu, Amy Pakyz, and Sam Hohmann. Together you helped me find my way, putting up guide posts to keep my research on track, while also allowing me to stumble and make it to the finish line on my own. Thank you for fostering my independence while providing guidance and encouragement. I appreciate your trust in me and am a better scientist because of you.

I gratefully acknowledge the funding that supported my PhD work, from both the Oregon Health & Science University – Portland State University School of Public Health, as well as my pre-doctoral award from the Oregon Clinical and Translational Research Institute (OCTRI).

This work would not have been possible without the support of the McGregor Research Group. I specifically thank Caitlin McCracken for being the clever research analyst that she is. Caitlin, you were instrumental in pulling together data and you never once let me down. You were also my number one cheerleader as I neared the end, and I will never forget your support. To Dr. Greg

Tallman for the countless hours you devoted to imparting your knowledge of organisms, susceptibilities, antibiotics, and clinical practice. Most importantly, thank you for never providing just a one-word answer to my many questions; you are an educator in the truest sense. To Drs. Kendall Tucker and Sara Gore, thank you for assisting with chart reviews and for so generously providing your clinical expertise. To Miriam and Brie, thank you for sharing your statistics and coding wisdom, and for the friendships we developed over the years. To Kirbee, my first friend and project partner in the PhD program: thank you for keeping it fun during the many late evening and early morning biostatistics project assignments.

To my fellow students in the Epidemiology PhD program, I am thankful for your friendships and for the comradery we developed over the years. Specifically, the Epi Girl Gang, I'm grateful for the Suki support group we established; for celebrating our successes and supporting each other through our many failures and rejections. Sarah Andrea, Kelly Reavis, Angela Senders, and Erin Takemoto: may the force be with you always.

And last but not least, thank you to my family and friends. You know who you are. I'm especially indebted to my family, for taking care of the children when I had evening classes or needed to work weekends. I would not be writing this page today if it were not for your unwavering support and unconditional love. Thank you for always being in my corner and for cherishing with me every milestone and achievement. Without you I would not have made it to the end.

And finally, to Maren and Lochlan: I am forever grateful for your enthusiastic enforcement of work/life balance.

ABSTRACT

Background: Each year, over 2 million infections and 23,000 deaths are caused by antibiotic-resistant bacteria in the United States. The prevalence of antibiotic resistance is increasing due to inappropriate and excessive antibiotic use. Hospitals maintain antibiotic stewardship programs as a method to promote judicious prescribing, yet identifying optimal targets for antibiotic use is challenging as it is dependent upon patient characteristics and regional prevalence of antibiotic resistance.

In 2015, the Centers for Disease Control and Prevention developed the Standardized Antimicrobial Administration Ratio (SAAR) to account for underlying differences in patient characteristics that differ between facilities and increase antibiotic use. Although significant effort went into the development of the SAAR metric, several aspects required scientific advancement: 1) the models were not externally validated, 2) SAAR risk-adjusts only for facility-level characteristics, meaning the validity and utility may be sub-optimal, and 3) there are no data to support that risk-adjusted antibiotic use rates are correlated with appropriate antibiotic use. In this dissertation, my objective was to validate and refine current antibiotic utilization metrics to better support stewardship efforts in the hospital.

Methods: In Aim 1, we used data from a nationwide network of hospitals to perform an external validation study of the SAAR metric. In Aim 2, we used the same dataset from Aim 1 to develop revised prediction models using patient-level characteristics to optimize risk-adjustment. In Aim 3, we constructed a retrospective cohort of adult patients admitted to a single facility to evaluate the

correlation between risk-adjusted antibiotic use and appropriate antibiotic use. For Aims 2 and 3, we focused on the SAAR metric for antibiotic agents predominantly used for resistant Gram-positive infections.

Results: In Aim 1, most predictors remained significant in the validation models. However, three predictors reversed direction and/or lost statistical significance. Overall the SAAR models performed moderately well when tested in an external dataset. In Aim 2, we found that diagnosis codes and other patient-level characteristics can be used to account for variability beyond what is explained through facility-level factors for predicting antibiotic use. In Aim 3, we observed minimal correlation between SAAR and the proportion of appropriate antibiotic use (Rho = 0.22; 95% CI -0.41, 0.70). Thus the relative performance of a single institution over time differed significantly when evaluated based on a risk-adjusted total antibiotic use metric compared to the proportion of appropriate use.

Conclusions: This dissertation work challenges the existing paradigm of the use of risk-adjusted antibiotic utilization metrics to inform stewardship practice. Risk-adjustment may be improved through use of patient-level characteristics in comparison to the current SAAR metric, which relies on facility-level variables. However, predicting antibiotic use at the patient-level is methodologically complex and additional work is needed to advance risk-adjustment methodology. Yet ultimately, our data suggest that risk-adjusted antibiotic use is not a valid proxy for appropriate use. Future research should focus on developing a valid metric that provides actionable evidence for stewardship programs in their efforts to improve antibiotic use in the hospital and limit spread of multidrug-resistant organisms.

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LIST OF ABBREVIATIONS

ASP	Antimicrobial Stewardship Program
AU	Antimicrobial Use
AUR	Antimicrobial Use and Resistance Module
CARB	Combating Antibiotic Resistant Bacteria
CDC	Centers for Disease Control and Prevention
CDI	Clostridioides difficile
CMS	Centers for Medicare and Medicaid Services
DOT	Days of therapy
ESBL	Extended-spectrum β-lactamase
GEE	Generalized estimating equation
HAI	Healthcare-associated infection
ICU	Intensive care unit
NHSN	National Healthcare Safety Network
MRSA	Methicillin-resistant *Staphylococcus aureus*
SAAR	Standardized Antimicrobial Administration Ratio
SIR	Standardized Infection Ratio
US	United States
WHO	World Health Organization

Chapter 1: Introduction and Research Aims

1.1 Introduction

Antibiotic resistance is a global threat to human health. By 2050, an estimated 10 million people worldwide will die annually from antibiotic-resistant bacteria unless a global response is mounted.[1] In the United States alone, there are over 2 million infections and 23,000 deaths caused by antibiotic-resistant bacteria each year.[2] Resistant bacterial infections are difficult to treat due to limited therapeutic options and are associated with increased patient morbidity and mortality. The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) each recently identified antibiotic resistance as one of the greatest threats to human health worldwide.[2,3]

Excessive and inappropriate antibiotic use in hospitalized patients is a significant, and modifiable, driver of antibiotic resistance.[4-7] Despite this awareness, hospitals continue to overuse certain antibiotics.[8-10] Up to 50% of antibiotics are prescribed sub-optimally,[11-15] meaning they are either unnecessary or excessively broad spectrum. Unlike for other classes of medications, the harms associated with this unnecessary or imprudent prescribing extends beyond the individual to impact the drug's effectiveness in other patients by fueling increasing antibiotic resistance. As such, judicious antibiotic use is essential in slowing the spread of resistant bacteria and improving the health and safety of both the individual patient and the population.

A critical component in combating antibiotic resistance within the acute care setting is the antimicrobial stewardship program (ASP). The WHO, United Nations,

CDC, and leading professional infectious disease societies support ASPs as a method to promote judicious antibiotic use and control the alarming spread of antibiotic-resistant bacteria. ASPs are specific programs and interventions whose purpose is “to monitor and direct antimicrobial use at a healthcare institution, thus providing a standard evidence-based approach to judicious antimicrobial use”.[16] Stewardship efforts focus on reducing unnecessary antibiotic use in hospitals and health systems and support the use of the correct agent, dose, duration, and route. Because of the large amount of antibiotics used in hospitalized patients, ASPs actively monitor antibiotic utilization, resistance, and adverse outcomes in order to make targeted interventions to improve patient care. However, ASPs have indicated that an inability to generate antibiotic use data has been an obstacle in the design of stewardship programs.[17] As with healthcare-associated infection rates, there is a desire to compare hospital performance against other facilities, a process known as benchmarking. However, the most appropriate metric for comparing antibiotic use between hospitals remains a topic of considerable debate.[18-20]

The CDC has identified that tracking antibiotic use is a core element of an effective ASP, as these data are necessary to identify areas for potential intervention.[21,22] To foster stewardship and encourage appropriate antibiotic use, benchmarks of judicious use are advised.[23] The current metric for benchmarking hospital performance is the CDC National Healthcare and Safety Network (NHSN) Standardized Antimicrobial Administration Ratio (SAAR),[24] which was endorsed by the National Quality Forum in 2015 for 3 years.[25] The metric assesses antibiotic

use in hospitals based on medication administration data that facilities collect electronically at the point of care and report through electronic file submissions to the NHSN. The SAAR is a ratio of observed-to-predicted antibiotic use, with predicted use values derived from regression-based indirect standardization using CDC-developed negative binomial regression models of antibiotic administration data. The antimicrobial use data used for this measure are antibiotic agents administered to adult and pediatric patients in a specified set of ward and intensive care unit (ICU) locations.

A major problem that complicates the use of benchmarking data is that there is wide variation in patient types and care delivered across hospitals. It is reasonable to expect greater antibiotic use at an academic health center than a rural community hospital caring for patients with less complicated conditions. Hence, risk adjustment is necessary for unbiased comparisons of antibiotic utilization between hospitals. However, regression modeling strategies for this purpose are still in their infancy.

While two iterations of SAAR models have been developed, the existing models have critical methodologic gaps that limit their utility for both stewardship teams and policy makers. First, the models have not yet been externally validated, and it is unknown if the models perform well in a dataset other than the one used to develop the models. Second, current SAAR models adjust only for a limited set of facility-level characteristics and do not take into account important patient-level characteristics that are known predictors of antibiotic use. Third, it is unknown if

comparing hospital performance based on risk-adjusted total antibiotic use is a valid proxy for appropriate antibiotic use.

1.2 Research Aims

The overall objective of this dissertation was to develop robust and valid antibiotic utilization metrics that best support hospital antimicrobial stewardship efforts. To achieve this objective, I completed the following research aims:

Research Aim 1 (Chapter 3): Validate the CDC Standardized Antimicrobial Administration Ratio (SAAR) as a measure for benchmarking inpatient antimicrobial use between hospitals. The Centers for Medicare and Medicaid Services (CMS) has proposed to include the SAAR for reimbursement purposes, but not without further validation and testing to ensure accurate and meaningful use of the measure. Using a retrospective dataset of inpatient encounters from a nationwide network of hospitals, I conducted a cross-sectional study to test the eternal validity of the SAAR models. I hypothesized that significant predictors identified by the CDC would remain statistically significant in an external dataset.

Research Aim 2 (Chapter 4): Develop revised antibiotic utilization prediction models to improve upon the risk adjustment provided by the current SAAR metrics. The risk adjustment methodology used for the SAAR models are limited to facility- and location-level predictors of antibiotic use. Using the same nationwide, patient-level data as in Aim 1, I leveraged a broad set of patient- and

facility level covariates to develop a new SAAR model for antimicrobial agents predominantly used for resistant Gram-positive infections. I hypothesized that the addition of new patient- and facility-level predictors would improve the performance of the current CDC SAAR model.

Research Aim 3 (Chapter 5): Evaluate the validity of antibiotic benchmarking based on risk-adjusted antibiotic use as a proxy for appropriate antibiotic use. CDC SAAR metrics utilize risk-adjusted measurement of antibiotic use and do not take into consideration the indication for use. To our knowledge, this study is the first to evaluate the validity of these metrics as a proxy for measuring appropriate antibiotic use. Using a one year retrospective cohort of patients from a single healthcare facility, I evaluated if the SAAR metric for antimicrobial agents predominantly used for resistant Gram-positive infections correlates with appropriate antibiotic use. I hypothesized that benchmarking rankings based on a total antibiotic use metric would be significantly different than rankings based on a measure of appropriate use.

Chapter 2: Review of the Literature

2.1 Introduction to antibiotic resistance

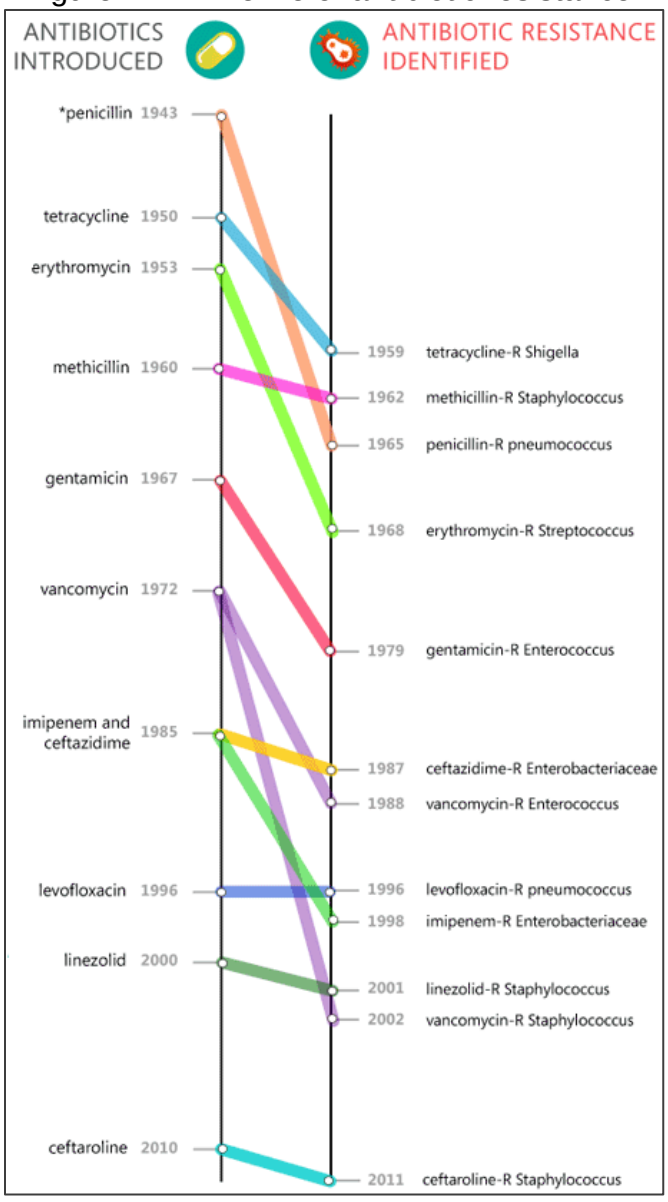
Antibiotics are among the greatest public health advancements of the 20th century.[26] However, shortly after the discovery of antibiotics, scientists warned of the dangers of antibiotic resistance; what was being celebrated as a prominent medical achievement was simultaneously becoming a great threat to public health.

2.1.1 Development of antibiotic resistance

Simply defined, antibiotic resistance is the ability of bacteria and other microorganisms to resist the effects of an antibiotic to which they were once susceptible.[27] As such, simply using antibiotics creates resistance. The biggest threat to the treatment of an infectious disease is that shortly after a new antibiotic is discovered and introduced, resistance to the antibiotic quickly follows (Figure 2.1). Unfortunately, resistance has developed for nearly all antibiotics. Penicillin was successful in treating bacterial infections among World War II soldiers in the 1940s; however, resistant bacterial strains soon emerged and the utility of penicillin was threatened.[28] In response, new beta-lactam agents were developed, restoring confidence in the efficacy of antibiotic therapy.[29] Yet the first case of methicillin-resistant *Staphylococcus aureus* (MRSA) was identified within the same decade, first in the United Kingdom in the early 1960s, and later in the United States (US) in 1968.[30] Vancomycin was introduced into clinical practice in 1972 as the preferred agent to treat infections caused by MRSA; however, some isolates quickly developed reduced susceptibility to this drug.[31-33] As bacterial infections have grown increasingly resistant to antibiotics, the pharmaceutical industry has

concurrently decreased its investment in research and development of new therapies[34,35] and the antibiotic pipeline is drying up.

Figure 2.1. Timeline of antibiotic resistance[2]



2.1.2 Major multi-drug resistant organisms

The combination of increasing antimicrobial resistance with a dry antibiotic pipeline has led to bacterial infections that are challenging, if not impossible, to treat.[36] Antibiotic-resistant infections lead to increased treatment failure and high

morbidity and mortality.[37,38] In 2013, the US Centers for Disease Control and Prevention (CDC) issued a report presenting the first snapshot of the public health burden and threats posted by antibiotic-resistant bacteria.[2] The negative impact on health is enormous: each year in the US there are over 2 million infections and 23,000 deaths caused by antibiotic-resistant bacteria.[2] Also outlined in the report are the top 18 drug-resistant threats to the US (Table 2.1). These bacterial threats are currently categorized by level of concern (urgent, serious, and concerning), and are grouped according to 7 criteria: clinical impact, economic impact, incidence, 10-year projection of incidence, transmissibility, availability of effective antibiotics, and barriers to prevention.[2] An urgent threat is one where the consequences of antibiotic resistance are high, posing a significant threat to patients and potentially developing into a significant public health concern. A serious threat may become an urgent threat, but antimicrobial therapies are frequently available for treatment of these bacteria. Finally, a concerning threat refers to bacteria with a low risk for antibiotic-resistance, but the CDC recommends that these bacteria be closely monitored.[2] Among the 15 urgent and serious threats, seven are bacteria predominantly acquired in the healthcare setting.[11]

Table 2.1. CDC pathogen threat levels[2]

Urgent	Serious				Concerning
CDI	*Acinetobacter*	ESBLs	Non-typhoidal *Salmonella*	MRSA	VRSA
CRE	*Campylobacter*	VRE	*Salmonella Typhi*	*Streptococcus pneumonia*	Group A *Streptococcus*
Neisseria gonorrhoeae	*Candida*	*Pseudo-monas aeruginosa*	Shigella	Tuberculosis	Group B *Streptococcus*

Abbreviations: CDC: Centers for Disease Control and Prevention; CDI: clostridioides difficile; CRE: carbapenem-resistant Enterobacteriaceae; ESBLs: extended-spectrum β-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin-resistant enterococci; VRSA: vancomycin-resistant *Staphylococcus aureus*

Clostridioides difficile infections (CDI) are the most frequent cause of healthcare-associated infections in the US[39] and are a manifestation of the unintended damage caused by antibiotic use.[40] CDI cause life-threatening diarrhea and occur primarily in individuals who have had both recent medical care and previous antibiotic use. A recent study estimated that the number of incident CDI cases in a single year in US patients was nearly half a million, and that it was associated with approximately 29,000 deaths.[41] Furthermore, CDI is associated with increased hospital length of stay,[42,43] readmissions,[44] and cost.[45,46] Incidence is higher in women and individuals older than 65 years, and an estimated 160,000 cases are community-associated and 293,000 are healthcare-associated.[41]

Extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae have been reported worldwide, most often in hospital settings but specimens have also been found in the community. ESBL are enzymes that confer resistance to most beta-lactam agents, including penicillins and cephalosporins. Studies examining clinical outcomes in patients with ESBL infections have shown increased mortality, length of stay, and hospital costs.[47-49] Prevalence rates vary between hospitals, and overall rates of ESBL infections have been increasing in the US; a recent study reported a doubling in the incidence of ESBL-producing infections (11.1% to 22.1% infections per 100,000 patient-days between 2009 and 2014).[50]

Methicillin-resistant Staphyloccocus aureus (MRSA) was identified in the early 1960s, shortly after the introduction of methicillin. Since then, MRSA has spread globally and may be acquired in both healthcare and community settings. MRSA can cause a wide spectrum of infections and is a prominent cause of purulent

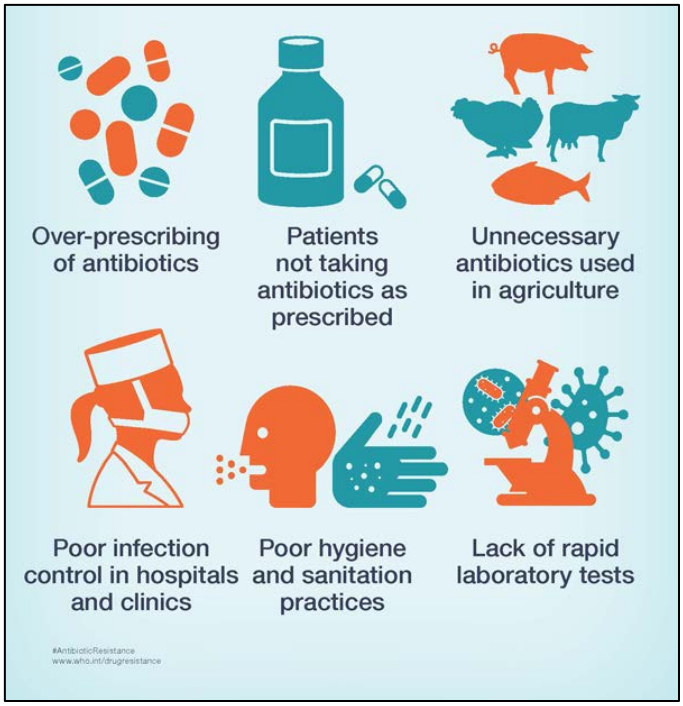
cellulitis.[51] The incidence of MRSA infections has recently declined among adults in the US, with the national estimated overall incidence of MRSA infections decreasing by 31% between 2005 and 2011.[52] The largest decrease was observed in hospital-onset infections (54% reduction), followed by healthcare-acquired community-onset infections (28%), and community-acquired infections (5%).[52]

Antibiotics are losing their effectiveness and few, if any, novel agents are expected to be developed soon. Therefore, it is imperative that the antimicrobial agents currently available are appropriately used and responsibly managed.

2.2 Key drivers of antibiotic-resistant bacteria

The development of antibiotic-resistant bacteria is a natural evolutionary response to antimicrobial exposure. At the societal level, complex and inter-related drivers increase the prevalence of antibiotic-resistant bacteria, primarily arising from antibiotic use in humans and in agriculture (Figure 2.2). Although the epidemiology of antibiotic resistance is complex, it is recognized that excessive and inappropriate use of antibiotics are important drivers in the emergence and spread of resistant bacteria.

Figure 2.2. Drivers of antibiotic-resistant bacteria[53]



2.2.1 Overuse. Antibiotics are among the most frequently prescribed medications and can be lifesaving drugs. However, simply using antibiotics is a key driver in the development of antibiotic resistance. Antibiotics are prescribed for the majority of hospitalized patients in the US, with upwards of 50% of patients receiving at least one dose during their hospital stay. In a study of 183 US hospitals representing over 11,000 inpatients, approximately half received at least one antimicrobial agent during their admission.[54] Another study found that nearly 2/3 of hospitalized patients received at least one dose of an antibiotic, with over 25% of patients receiving two or more agents.[8] A large systematic review and meta-analysis found an association between antibiotic consumption and development of antibiotic resistance, and that increased antibiotic use not only produces resistance at the individual patient level but also resistance in the broader community.[4] While there is heterogeneity in the literature regarding overall trends in hospital antibiotic use, studies have also shown rates of broad-spectrum agent use to be on the rise.[9,10,55]

2.2.2 Inappropriate use. In addition to antibiotic overuse, inappropriate use is another key driver of the development of antibiotic-resistant bacteria. Inappropriate

use is defined as “use of antimicrobials in the setting of established infection to which the pathogen is resistant or use of antimicrobials not recommended in treatment guidelines.”[56] Antibiotic use may also be considered unnecessary, such as in circumstances where it is prescribed for viral or other non-infectious conditions, when the days of prescribed therapy extend beyond the indicated duration of treatment, or when empiric broad-spectrum coverage is continued when microbiology results indicate a narrower-spectrum agent would adequately treat the infection. Furthermore, antibiotic therapy may be considered suboptimal if either the drug choice, route, and/or dose can be optimized.[56] Approximately 20-50% of antibiotic use in hospitals may be inappropriate, unnecessary, or suboptimal.[10,11,13-15,57] This is harmful because unlike other classes of medications, misuse of an antibiotic in one patient affects the microbial environment and thereby impacts the drug’s effectiveness in other patients and thereby society.

2.3 Improving antibiotic use is a national priority

In response to the growing antibiotic resistance crisis, in 2014 US President Obama issued Executive Order 13676,[58] mandating the US government issue a National Strategy for Combating Antibiotic Resistant-Bacteria[59] and directing the development of a National Action Plan.[60] Prior to this, national and international organizations had identified antibiotic resistance as a major public health problem. In 2012, the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) collectively issued a policy statement calling for the development and dissemination of antimicrobial stewardship programs (ASPs),

defined as “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration.”[61] The primary goal of antimicrobial stewardship is “to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance.”[57] Subsequently in 2015, The Joint Commission, an independent non-profit organization that accredits and certifies nearly 21,000 healthcare organizations across the US, developed the antimicrobial stewardship standard for hospitals.[62] Most recently, the Joint Commission announced a new requirement, the Medication Management standard, which became effective in January 2017 and requires hospitals, critical access hospitals, and nursing care centers to have “an antimicrobial stewardship program based on current scientific literature.”[63]

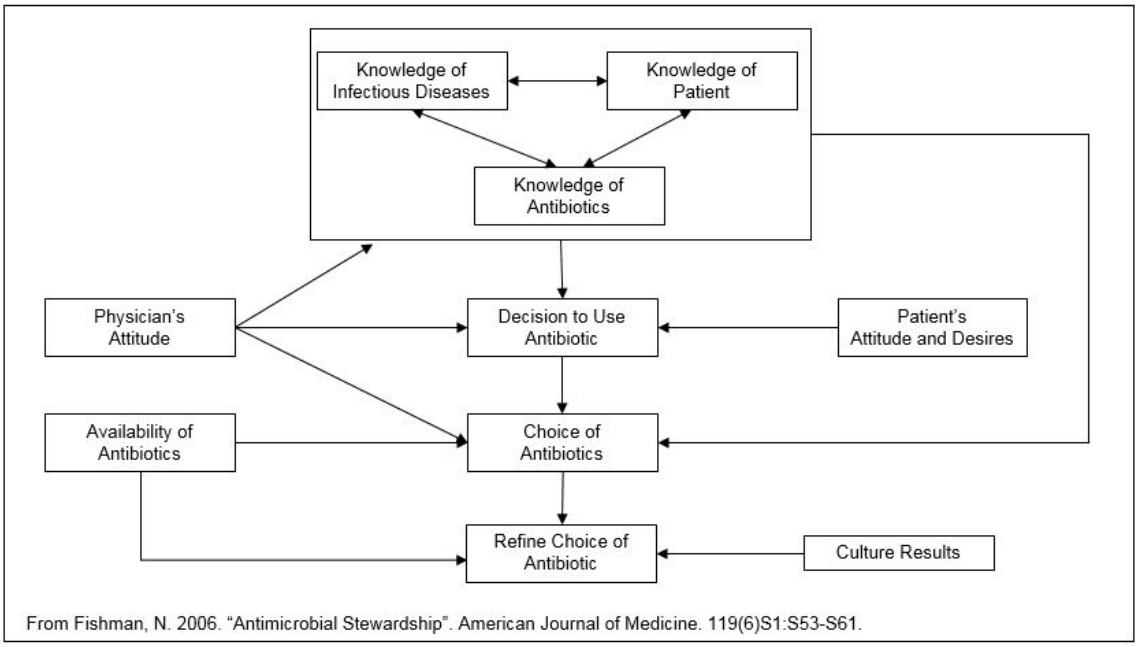
2.4 Antimicrobial stewardship to prevent emergence and spread of antibiotic resistance

Antimicrobial stewardship refers to a coordinated approach to ensure optimal prescribing of antimicrobial agents. ASPs are recommended by several clinical, professional, and public health organizations[11,22,64-66] and are a key component of the National Strategy for Combating Antibiotic-Resistant Bacteria in the US. The CDC recommends that all hospitals implement ASPs that include seven core elements: 1) leadership commitment; 2) accountability through a single physician lead; 3) drug expertise through a single pharmacist; 4) specific interventions to improve prescribing; 5) tracking of patterns of antibiotic prescribing

and resistance; 6) reporting antibiotic use and resistance information to providers; and 7) education.[67] ASPs include a variety of interventions, including pre-authorization and/or prospective audit, antibiotic-timeouts, restriction of specific antibiotics or treatment duration, antibiotic cycling or mixing, and education.[67,68] Example interventions include discontinuing unnecessary antibiotic treatment for asymptomatic bacteriuria, or limiting the use of agents associated with a high risk of subsequent *Clostrioides difficile* infection.

Antimicrobial stewardship involves "selecting the most appropriate drug at its optimal duration of therapy to eradicate an infection while minimizing side effects and pressures for the selection of resistant strains."[69] A provider's decision to prescribe an antibiotic and select the appropriate agent for the correct duration is guided by several factors (Figure 2.3). Thorough understanding of infectious diseases and the pathogens involved in specific infections, as well as knowledge of susceptibility patterns and pharmacokinetics is critical. Other factors underpinning the decision to prescribe an antibiotic include physician attitude, availability of antibiotics, culture results, and patient attitude and preferences.

Figure 2.3. Conceptual framework for antibiotic use[70]



There is a growing body of evidence that hospital-based interventions aimed at optimizing inpatient antibiotic prescribing through ASPs improves patient outcomes.[71] Several studies have shown that antibiotic stewardship programs improve patient safety by significantly reducing rates of hospital-acquired CDI, reducing treatment failures, and increasing the frequency of optimal prescribing.[72-77] While more rigorous research is needed, a recent meta-analysis of 32 studies indicates that ASPs may also reduce the incidence of infection and colonization due to antibiotic resistant bacteria and CDI among hospital inpatients.[78] Specifically, this meta-analysis found ASPs to be associated with reduced incidence of multi-drug resistant Gram-negative bacteria (51% reduction), ESBLs (48%), MRSA (37%), and CDI (32%).[78] It has also been well documented that ASPs are highly cost effective.[57,79-81] However, studies examining the cost savings of stewardship programs have primarily focused on direct pharmacy costs. When

other outcomes such as reduced length of stay and readmission are taken into account, the potential savings may be even more dramatic.[65]

Despite the promise of ASPs in improving patient care and safety, findings from a recent CDC annual hospital survey found ASP implementation to be variable across the US. Less than 40% of hospitals surveyed in 2014 met each of the 7 core elements, and the percent of hospitals in each state that reported all seven elements ranged from 7-58%.[82] Meeting all core elements was associated with increased hospital size, teaching status, facility type (surgical specialty or critical access less likely than pediatric and general acute care), and salary and administrative support for antimicrobial stewardship. Viewed optimistically, more than 50% of hospitals reported the presence of antimicrobial stewardship infrastructure. Increased outreach to hospitals and guidance on program implementation may improve progress toward achieving national goals.[83]

2.5 Benchmarking in infectious disease

Guidelines for developing ASPs recommend that hospitals measure their antimicrobial use and then compare their use, after risk-adjustment, to that of other facilities.[57] The purpose of risk-adjustment is to determine the proportion of antibiotic use that is accounted for by “non-modifiable” factors, such as patient mix, allowing for critical examination of the remaining variability in use. In some circumstances, remaining variation may be due to a deficit in quality of care, such as inappropriate and/or excessive use, and may indicate areas in which stewardship programs can target their interventions. The purpose of inter-hospital

comparisons, also known as “benchmarking”, is to improve healthcare by highlighting strengths and weaknesses, stimulating competition, and assessing effectiveness of interventions to reduce infections and antibiotic use.[84] The National Healthcare Safety Network (NHSN) is the public health surveillance system that the CDC maintains as a mainstay of its healthcare-associated infection (HAI) prevention program and is the mechanism by which monitoring, tracking, and benchmarking activities are facilitated.[85]

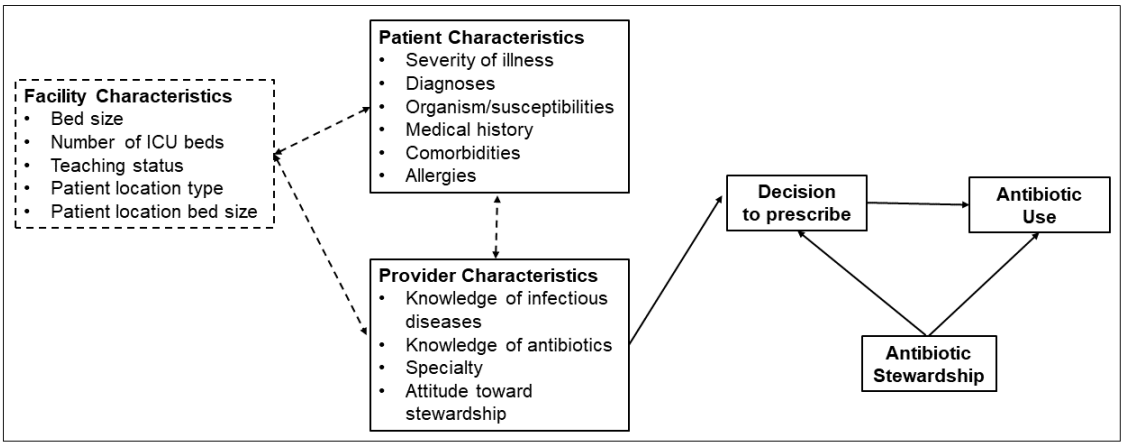
The Standardized Infection Ratio (SIR) is the primary summary measure used by the NHSN to track healthcare-associated infections (HAI). The SIR is a patient safety metric used to compare outcomes across multiple locations over time by risk-adjusting for differences in hospital size, teaching status, intensive care unit (ICU) size and type (which are factors seen as surrogates for patient severity).[86] The SIR is a ratio of observed-to-predicted infections, with the predicted number of infections (the denominator) calculated using multivariable regression models generated from nationally aggregated data during a baseline time period. The SIR allows comparisons between the number of infections ***observed*** within a facility, region, or state to the number of infections ***predicted***. This indirect standardization approach allows comparison to the national benchmark which facilities can use to track HAI outcomes over time.

In 2011, as part of the Antimicrobial Use and Resistance Module (AUR), the NHSN released the Antimicrobial Use (AU) option to provide an additional mechanism for facilities to monitor their ASP efforts. The AU option is currently voluntary, and facilitates the reporting and analysis of antimicrobial use at

participating hospitals. Modeled after the SIR, the NHSN developed the Standardized Antimicrobial Administration Ratio (SAAR) in 2014 to provide summary data that hospitals, healthcare systems, and public health agencies can use for benchmarking antibiotic use and as a guide for evaluating stewardship programmatic performance.[87] In January 2016, the National Quality Forum endorsed the SAAR for three years as an inpatient quality measure, permitting hospital benchmarking of antibiotic use.[25] Shortly afterwards, the CDC released a second iteration of risk-adjusted metrics, the 2017 SAAR models.[88]

However, risk-adjusted benchmarking of antibiotic use is still an emerging field. Figure 2.4 displays the key factors that influence the decision to prescribe an antibiotic, thus impacting overall antibiotic use. As such, these are important factors to consider in risk-adjustment. The clinical factors most proximal to the decision to prescribe include patient and provider characteristics. Patient characteristics include severity of illness, diagnoses, and comorbidities, and are factors that should be accounted for in a risk-adjusted benchmarking metric. Further upstream are facility characteristics, such as hospital bed size, number of ICU beds, teaching status, and patient location type (e.g. medical ward), which serve as proxies for patient and provider characteristics. These facility-level characteristics are currently the only factors considered in the risk-adjusted SAAR metric; patient characteristics are not yet included in the models. As such, it is unknown whether the risk-adjustment adequately accounts for differences in patient mix that vary across facilities and affect antibiotic use.

Figure 2.4. Risk-adjustment of factors that influence antibiotic use



A variety of studies have investigated benchmarking of antibiotic use, with notable variation in hospital populations, measures of antibiotic utilization, and factors used in risk-adjustment.[19,89-94] As such, no established standards exist for risk-adjusted benchmarking of antibiotic use in hospitalized patients. While many methodological challenges remain and clinical outcomes have yet to be determined, benchmarking antimicrobial use is set to become a critical component of ASP activities. This dissertation research challenges the existing paradigm of the use of current risk-adjusted antibiotic utilization metrics to inform stewardship practice.

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Chapter 3: Evaluating the Performance of the Centers for Disease Control and Prevention (CDC) Standardized Antimicrobial Administration Ratios (SAARs)

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3.1 Abstract

Background: The Centers for Disease Control and Prevention (CDC) through the National Healthcare Safety Network (NHSN) have developed Standardized Antimicrobial Administration Ratios (SAARs) for risk-adjusted comparisons of hospital antibiotic use. SAAR is a ratio of observed-to-predicted antibiotic use, with predicted values derived from regression models. The true test of a model's predictive validity is how well it performs with new data. The objective or our study was to evaluate the performance of SAAR regression models in an independent cohort of nationwide facilities.

Methods: We used retrospective data from inpatient encounters at facilities contributing pharmacy data to the Vizient Clinical DataBase and Resource Manager (CDB/RM^{TM}) between January 1, 2016 and December 31, 2016. Facility antibiotic use was reported as days of therapy per 1,000 days present. We constructed negative binomial regression models for each of the five categories of antibiotic use (broad-spectrum agents used for hospital onset/multidrug resistant organism infections; broad-spectrum agents predominantly used for community-acquired infections; anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents; agents predominantly used for surgical site infection (SSI) prophylaxis; and all antibiotic agents). Each model included only the significant predictors identified by the CDC for each respective SAAR model: intensive care unit (ICU), teaching status, and patient location. We contrasted our models with the CDC models, evaluated predictor effect size and significance ($p<0.05$) and assessed model fit using deviance-based pseudo R^2.

Results: Our cohort included 3,780,056 inpatient encounters from 145 facilities. Predictors identified as significant by the CDC remained significant in all models except for medical location type in the model for agents used for hospital-onset/multidrug-resistant infections (p=0.20), the interaction between ICU and medical/surgical location type in the anti-MRSA agent model (p=0.33), and ICU status in the SSI prophylaxis model (p=0.11). Although not statistically significant, two of the coefficients changed direction. The deviance-based pseudo R^2 values were low across models, ranging from 0.01 to 0.05.

Conclusions: Overall, risk-adjustment with facility-level predictors resulted in moderate performance of SAAR models. Future research should explore whether the addition of a broader set of patient- and facility-level predictors improve the fit of the current SAAR models, thus providing more meaningful inter-hospital comparisons of antibiotic use.

3.2 Introduction

Each year in the United States there are over 2 million infections and 23,000 deaths caused by antibiotic resistant bacteria,[1] signaling a grave public health threat posed by antibiotic resistance. Resistant bacterial infections are difficult to treat due to limited therapeutic options and are associated with increased morbidity and mortality. The Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, and the Pediatric Infectious Diseases Society collectively issued a policy statement calling for the development and dissemination of antimicrobial stewardship programs (ASPs) as one method for

combating the growing threat of antimicrobial resistance.[2,3] Subsequently, the Joint Commission implemented the antimicrobial stewardship standard for hospitals, which requires acute care and critical access hospitals to have “an antimicrobial stewardship program based on current scientific literature.”[4]

The Centers for Diseases Control and Prevention (CDC) has identified that tracking antimicrobial use is a core element of an effective ASP and that hospitals conduct periodic assessments of their antibiotic use.[5] However, in the 2016 NHSN annual survey, stewardship teams indicated that an inability to analyze antibiotic utilization data has been an obstacle in designing interventions.[6] The CDC responded to this need by broadening the scope of an existing surveillance system, the National Healthcare Safety Network (NHSN), to include the Antibiotic Use (AU) Option. This provides a mechanism for facilities to monitor their antibiotic use and benchmark performance against peer institutions; however, direct comparison of antibiotic use between hospitals is complicated by differences in underlying patient and hospital characteristics.

In 2016, the CDC released a new metric for measuring and benchmarking antibiotic use, the Standardized Antimicrobial Administration Ratio (SAAR). Akin to the Standardized Infection Ratio (SIR) for assessing healthcare-associated infections, the SAAR is a ratio of observed-to-predicted antibiotic use, where predicted use is derived from regression-based indirect standardization models developed from national antibiotic use data.[7] While significant effort has gone into the development of the SAAR and facilities are currently using the metric to evaluate antibacterial utilization,[8,9] the models have not yet been externally

validated. The Centers for Medicare & Medicaid Services (CMS) has proposed including SAAR metrics in the Hospital Inpatient Quality Reporting program, but not without validation and testing to ensure accurate and meaningful use of the measure.[10] The objective of our study was to compare the performance of the 2014 version of SAAR regression models in an independent cohort of nationwide hospitals.

3.3 Methods

3.3.1 Data source

We conducted a cross-sectional, external validation study using retrospective data from inpatient encounters at facilities contributing pharmacy data to the Vizient Clinical DataBase and Resource Manager (CDB/RM™). The CDB/RM™ is a comparative database used by approximately 160 member hospitals to evaluate both internal and network performance, and as a tool to benchmark against peer hospitals to improve performance.[11] The CDB/RM™ contains procedure- and diagnosis-specific data from charge transaction masters and inpatient billing files. The database also contains data on demographics, diagnoses, procedures, and laboratory results for each hospital discharge.

3.3.2 *Inclusion and exclusion criteria*

All inpatient hospital encounters between January 1, 2016 and December 31, 2016 were included. Facilities without antibiotic use data reported for all 12 months of 2016 were excluded.

3.3.3 SAAR antimicrobial agent categories

The CDC created five different categories of antimicrobial agents according to the most common clinical uses of each agent: A) broad-spectrum agents predominantly used for hospital-onset/multi-drug resistant organism (MDRO) infections, B) broad-spectrum agents predominantly used for community-acquired infections, C) anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents, D) agents predominantly used for surgical site infection (SSI) prophylaxis, and E) all antibiotic agents.[7] Using CDB/RM^{TM} data, we collapsed antimicrobial agents into the same antibiotic categories to replicate the CDC groupings.

3.3.4 Risk-adjustment covariates

Covariates used in the calculation of predicted antibacterial use varies for the SAAR metric for each antibacterial group (Table 3.1). We mapped patient movement in the Vizient data to the NHSN-defined patient care locations:[12] Intensive Care Unit (ICU) (yes/no) and patient location (ICU/ward, medical, medical/surgical, surgical, pediatric). Facility teaching status was based upon membership in the Association of American Medical Colleges Council of Teaching Hospitals and Health Systems.

3.3.5 Antibiotic use outcome

Facility antibiotic use was calculated as days of therapy (DOT) per 1,000 days present, analogous to the NHSN definition.[13] We used Admission/Discharge/Transfer (ADT) data to calculate days present in each NHSN patient care location. For each facility, DOT (the numerator) and days present (the denominator) were aggregated to the year level for each patient care location from

encounter-level data. Encounter-level data were then aggregated to the facility-level.

3.3.6 Statistical Analysis

To evaluate external validity of the SAAR metrics, we constructed multivariable regression models for each SAAR antibacterial category. Each model included only the covariates used to calculate predicted antibacterial use for each respective SAAR (Table 3.1).[7] Our sample of antibiotic use data in the CDB/RM™ exhibited overdispersion; thus, we constructed negative binomial regression models to account for this overdispersion for each of the five SAAR antibiotic categories. We explored the correlation structure of encounters within hospitals, and for models in which we identified correlation, we used a mixed effects negative binomial model with facility specified as a random effect.

We contrasted our models with the CDC models used to develop the SAAR metrics, evaluated predictor effect size and significance, and assessed model fit using a deviance-based pseudo R^2.[14] P-values were two-sided and values <0.05 were considered statistically significant. To evaluate precision, 95% confidence levels were also calculated. Models for data without correlation were constructed using the SAS® genmod procedure; where we identified correlation, the SAS® glimmix procedure was used to account for the correlation. All analyses were performed using SAS® software version 9.4.[15]

3.4 Results

Of 157 facilities with pharmacy data in the CDB/RM^{TM}, 145 had complete reporting across all 12 months of 2016 and were included in our study. The cohort included 3,780,056 inpatient encounters between January 1, 2016 and December 31, 2016. Approximately 65% of facilities were teaching hospitals, 67% had a transplant service, and 40% were located in the Midwestern region (Table 3.2).

We identified correlation in two groups of antibiotic use (broad-spectrum agents predominantly used for hospital-onset/MDRO infections and anti-MRSA agents) and therefore used mixed effects to model the data. The other three antibiotic groups did not exhibit correlation and were modeled only using fixed effects. The magnitude and direction of the predictors for each of the five validation models are displayed in Figures 3.1-3.5 along with the corresponding values from the CDC's 2014 development models.[7] All SAAR risk-adjustment covariates identified as significant by the CDC remained significant in the validation data except for three covariates (Table 3.3): 1) medical location in the model predicting use of broad-spectrum agents predominantly used for hospital-onset/MDRO infections (coefficient estimate=-0.08 (95% CI -0.20, 0.04; p=0.20); 2) the interaction between ICU and medical/surgical location in the model predicting use of anti-MRSA agents (coefficient estimate=0.56 (95% CI -0.59, 1.72; p=0.34); and 3) ICU status in the model predicting use of agents predominately used for surgical site infection prophylaxis (coefficient estimate=0.11 (95% CI -0.03, 0.25; p=0.11). Two predictors reversed direction in the validation models, however they were not statistically significant.

The deviance-based pseudo R^2 values were consistently low across both the validation and CDC SAAR models (Table 3.4). Similar to the R^2 for linear models, higher values reflect better model performance. However the magnitude of pseudo R^2 measures are much lower and a pseudo R^2 value between 0.2 and 0.4 represents a model with very good fit.[16] Among the validation models, the best fit was observed for the all antibiotic agents model (pseudo R^2=0.024) and the poorest was the model predicting use of agents predominately used for surgical site infection prophylaxis (pseudo R^2=0.018). Similar low values were observed for the CDC models, with pseudo R^2 values ranging from 0.011 (broad-spectrum agents predominantly used for community-acquired infections) to 0.052 (broad-spectrum agents predominantly used for hospital-onset/MDRO infections). The model fit statistics for two of the validation models (broad-spectrum agents predominantly used for hospital-onset/multi-drug resistant infections and anti-MRSA agents) required a mixed effects negative binomial model to account for the correlation structure in the CDB/RM^{TM} data. As such, metrics comparable to the corresponding CDC models could not be generated.

3.5 Discussion

The purpose of a risk-adjusted antibiotic use metric is to account for the effects of patient mix and facility differences so that facilities can compare antibiotic use attributable to practice change. By adjusting for non-modifiable risk factors, any remaining differences in antibiotic use can then be more easily attributed to

differences in hospital performance. As such, the methods used to derive predicted antibiotic use (the denominator of the SAAR metric) are critically important.

To test the external validity of the 2014 SAAR metrics, we compared the performance of the CDC prediction models in an independent cohort of nationwide hospitals. Overall, we observed that risk-adjustment with facility-level predictors resulted in moderate performance of the CDC SAAR models based on similarities between the two sets of models. Most models produced similar effect measures overall; however, three predictors of antibiotic use were no longer significant in the external dataset, and, although not statistically significant, two of these coefficients changed direction. Furthermore, four of the five models had at least one predictor with non-overlapping confidence intervals when evaluated in the external dataset. Finally, both the CDC and validation models had poor fit across all five antibiotic categories as evidenced by the low deviance-based pseudo R^2 values. It is known that prediction models tend to perform poorer in an external validation dataset when compared to the development dataset,[17] which we observed in this study. However, the true test of a model's predictive validity is how well it performs with new data. To our knowledge, this is the first study to evaluate the external validity of the SAAR models.

The CDC has identified that monitoring antibiotic use is a core element of a successful stewardship program and has indicated that benchmarking antibiotic use is a high priority for the US.[5,18] Valid risk-adjustment is therefore essential to ensure fair comparison of antibiotic use across hospitals, yet methods for risk-adjustment of antibiotic use are variable and debated.[19-23] If predicted values

generated from the SAAR regression models are not valid, stewardship teams are unable to accurately identify areas in which they should target interventions. Additionally, ASPs may needlessly allocate resources to intervene on a misleading SAAR value when in fact no intervention is necessary.

There are several limitations to our study. First, the CDB/RM™ data repository contains administrative claims data, not electronic medication administration record or bar-coded medication administration data as in the NHSN. This may result in an overestimate of antibiotic use because some antibiotics that were ordered may not have been administered; however we expect this would be non-differential. Second, classification of patient location was performed by our investigator team based upon accommodations data submitted to Vizient and may differ from how each facility would classify their locations for NHSN. To minimize any potential biases introduced by this subjective approach to mapping patient care locations, we incorporated diagnosis-related group (DRG) codes to map patients to the location(s) where they likely received care during their encounter. Third, due to correlation identified in the data for two of the five validation models, we used a different modeling approach than the one undertaken by the CDC and thus cannot compare model fit. Finally, 12 facilities were just beginning to report data to the CDB/RM™ during 2016 and were excluded due to incomplete reporting of antibiotic use data across all months of the study period. However, characteristics of excluded hospitals were similar to those of included hospitals; as such it is unlikely that the exclusions would have biased our results.

In 2017 the CDC released a second iteration of SAAR models, which hopefully improves upon the risk-adjustment of the models validated in this study. However, details of the new models are not yet published in the peer-reviewed literature and therefore their validity unknown. As such, the SAAR models assessed in this study are the only models with data available for validation purposes. Ongoing efforts to validate or recalibrate the SAAR models should focus on patient location type covariates (e.g. medical unit, ICU location) as these same patient location types are again used as predictors in the 2017 CDC SAAR models. To effectively direct hospital stewardship programs, it is critical that metrics for monitoring and evaluating antibiotic use are valid. Incorporating a broader set of facility- or patient-level predictors may improve the fit of the CDC SAAR models, thus providing more meaningful inter-hospital comparisons of antibiotic use.

Tables and Figures

Table 3.1. Significant predictors included in CDC SAAR models, by antimicrobial agent category

Antimicrobial agent category	Significant predictors
A. Broad-spectrum agents predominantly used for hospital-onset/MDRO infections	ICU, 4-way location type variable[b]
B. Broad-spectrum agents predominantly used for community-acquired infections	Teaching status, ICU, pediatric location
C. Anti-MRSA agents	ICU, 4-way location type variable[b], interaction term: ICU and 4-way location type variable[b]
D. Agents predominantly used for surgical site infection prophylaxis[a]	ICU, surgical location
E. All antibiotic agents	ICU, 4-way location type variable[b]

[a] Intravenous administrations only
[b] Levels: medical unit, medical/surgical unit, surgical unit, pediatric unit (referent)
Abbreviations: CDC: Centers for Disease Control and Prevention; ICU: intensive care unit; MDRO: multi-drug resistant organism; MRSA: Methicillin-resistant Staphylococcus aureus; SAAR: Standardized Antimicrobial Administration Ratio

Table 3.2. Characteristics of included hospitals (N=145)

Characteristic	Vizient hospitals (n (%))
Region	
New England/Mid-Atlantic	46 (31.7)
Southeast	22 (15.2)
Midwest/Mid-Continent	58 (40.0)
West	19 (13.1)
Teaching hospital[a]	94 (64.8)
Embedded pediatric hospital	50 (34.5)
Bed size	
1-249	31 (21.4)
250-499	31 (21.4)
500-749	53 (34.5)
750+	30 (20.7)
Level 1 Trauma Center[b]	65 (44.8)
Transplant service[c]	97 (66.9)
Case Mix Index	
0-1.49	18 (12.4)
1.5-1.99	51 (35.2)
2.0+	76 (52.4)

[a]Teaching status based on Association of American Medical Colleges Council of Teaching Hospitals and Health Systems membership
[b]Levels defined per the American Trauma Society
[c]Facility has a transplant service if it performs one or more of the following transplants: heart, lung, heart/lung, intestinal, kidney, liver, pancreas

Table 3.3. Comparison of risk model coefficient estimates, by antimicrobial agent category

	CDC Estimate (95% CI)	P value	Validation Estimate (95% CI)	P value
Model A: Broad-spectrum agents predominantly used for hospital-onset/MDRO infections				
Intercept	-2.67 (-2.83, -2.51)	<0.0001	-2.72 (-2.84, -2.61)	<0.0001
ICU	0.97 (0.87, 1.07)	<0.0001	0.94 (0.84, 1.04)	<0.0001
Location Type: Medical Unit *	0.52 (0.35, 0.70)	<0.0001	-0.08 (-0.20, 0.04)	0.1956
Location Type: Medical/Surgical Unit	0.44 (0.27, 0.62)	<0.0001	0.36 (0.19, 0.52)	<0.0001
Location Type: Surgical Unit	0.41 (0.21, 0.60)	<0.0001	0.17 (0.02, 0.32)	0.025
Location Type: Pediatric Unit	REF	--	REF	--
Model B: Broad-spectrum agents predominantly used for community-acquired infections				
Intercept	-1.76 (-1.86, -1.66)	<0.0001	-2.05 (-2.17, -1.92)	<0.0001
Teaching Status	-0.38 (-0.48, -0.27)	<0.0001	-0.24 (-0.39, -0.10)	0.0009
ICU	0.12 (0.03, 0.22)	0.013	0.36 (0.23, 0.48)	<0.0001
Pediatric Location	-0.20 (-0.36, -0.05)	0.011	-1.09 (-1.23, -0.95)	<0.0001
Model C: Anti-MRSA agents				
Intercept	-3.51 (-3.70, -3.32)	<0.0001	-3.66 (-3.85, -3.48)	<0.0001
ICU	1.43 (1.02, 1.84)	<0.0001	1.20 (0.96, 1.44)	<0.0001
Location Type: Medical Unit	1.05 (0.84, 1.26)	<0.0001	1.26 (1.03, 1.49)	<0.0001
Location Type: Medical/Surgical Unit	0.89 (0.68, 1.11)	<0.0001	1.22 (0.98, 1.46)	<0.0001
Location Type: Surgical Unit	1.10 (0.85, 1.34)	<0.0001	1.85 (1.58, 2.12)	<0.0001
Location Type: Pediatric Unit	REF	--	--	--
Interaction of ICU and Location Type: Medical Unit	-0.52 (-0.97, -0.08)	0.021	-0.39 (-0.69, -0.08)	0.0129
Interaction of ICU and Location Type: Medical/Surgical Unit *	-0.54 (-0.99, -0.09)	0.018	0.56 (-0.59, 1.72)	0.3364
Interaction of ICU and Location Type: Surgical Unit	-0.84 (-1.31, -0.36)	0.001	-0.75 (-1.13, -0.37)	0.0001
Interaction of ICU and Location Type: Pediatric Unit	REF	--	REF	--
Model D: Agents predominantly used for surgical site infection prophylaxis				
Intercept	-3.29 (-3.40, -3.18)	<0.0001	-2.83 (-2.92, -2.74)	<0.0001
ICU *	0.34 (0.15, 0.54)	0.001	0.11 (-0.03, 0.24)	0.1103
Surgical Location	0.97 (0.74, 1.19)	<0.0001	1.20 (1.03, 1.37)	<0.0001
Model E: All antibiotic agents				
Intercept	-0.79 (-0.89, -0.68)	<0.0001	-1.23 (-1.31, -1.14)	<0.0001
ICU	0.50 (0.43, 0.57)	<0.0001	0.64 (0.55, 0.72)	<0.0001

Location Type: Medical Unit	0.17 (0.05, 0.28)	0.004	0.59 (0.49, 0.69)	<0.0001
Location Type: Medical/Surgical Unit	0.18 (0.06, 0.29)	0.003	0.76 (0.62, 0.89)	<0.0001
Location Type: Surgical Unit	0.14 (0.01, 0.27)	0.030	0.96 (0.84, 1.08)	<0.0001
Location Type: Pediatric Unit	REF	--	REF	--

*Coefficient weight changed direction and/or not significant in Validation data

Abbreviations: CDC: Centers for Disease Control and Prevention; ICU: intensive care unit; MDRO: multi-drug resistant organism; MRSA: methicillin-resistant *Staphylococcus aureus*

Table 3.4. Fit of Vizient and CDC SAAR models, by antimicrobial agent category

Model	Deviance-based Pseudo R^2	
	Vizient	CDC
A. Broad-spectrum agents predominantly used for hospital-onset/MDRO infections[a]	--	0.052
B. Broad-spectrum agents predominantly used for community-acquired infections	0.019	0.011
C. Anti-MRSA agents[a]	--	0.049
D. Agents predominantly used for surgical site infection prophylaxis[b]	0.018	0.019
E. All antibacterial agents	0.024	0.029

[a] Deviance-based pseudo R^2 metrics not calculated for Models A and C because of correlation in the data

[b] Intravenous administrations only

Abbreviations: CDC: Centers for Disease Control and Prevention; MDRO: multi-drug resistant organism; MRSA: methicillin-resistant *Staphylococcus aureus*

Figure 3.1. Comparison of coefficient estimates for CDC and Validation models for broad-spectrum agents predominantly used for hospital-onset/multidrug-resistant infections

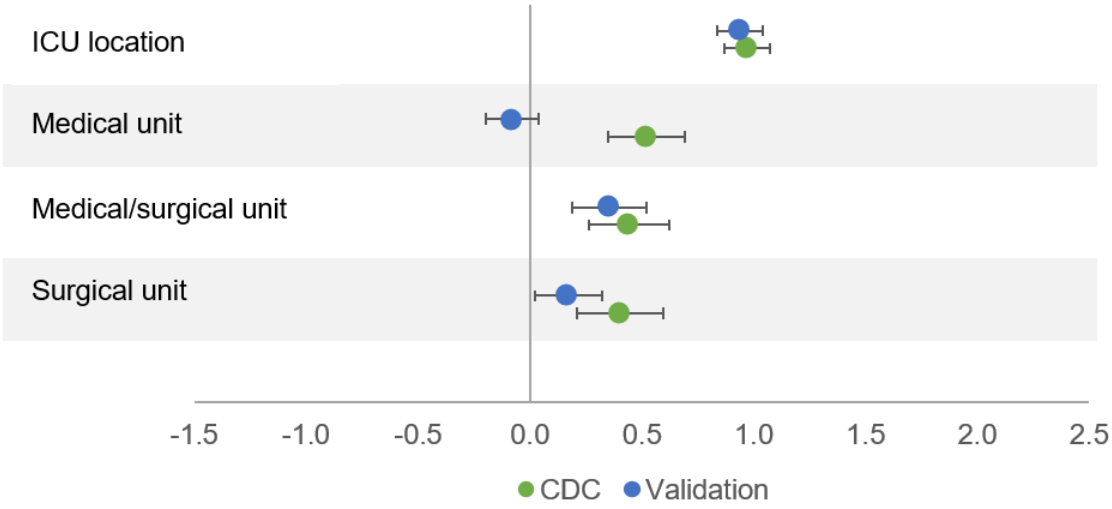


Figure 3.2. Comparison of coefficient estimates for CDC and Validation models for broad-spectrum agents predominantly used for community-acquired infections

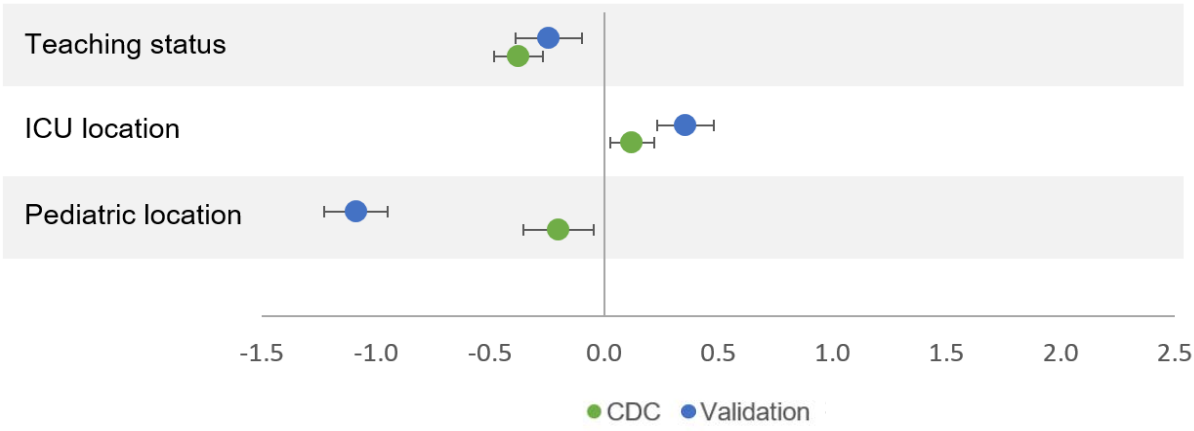


Figure 3.3. Comparison of coefficient estimates for CDC and Validation models for anti-MRSA agents

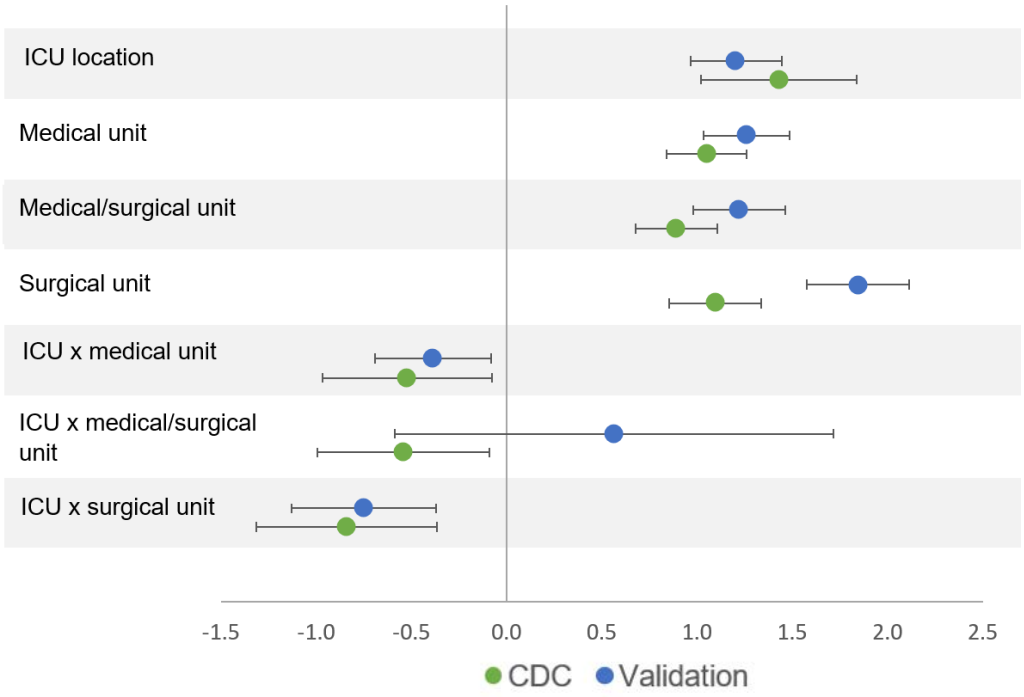


Figure 3.4. Comparison of coefficient estimates for CDC and Validation models for agents predominantly used for surgical site infection prophylaxis

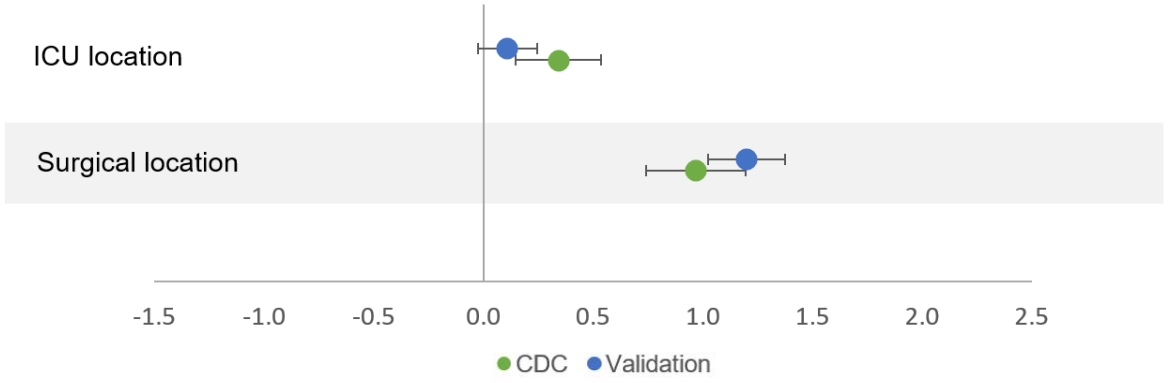
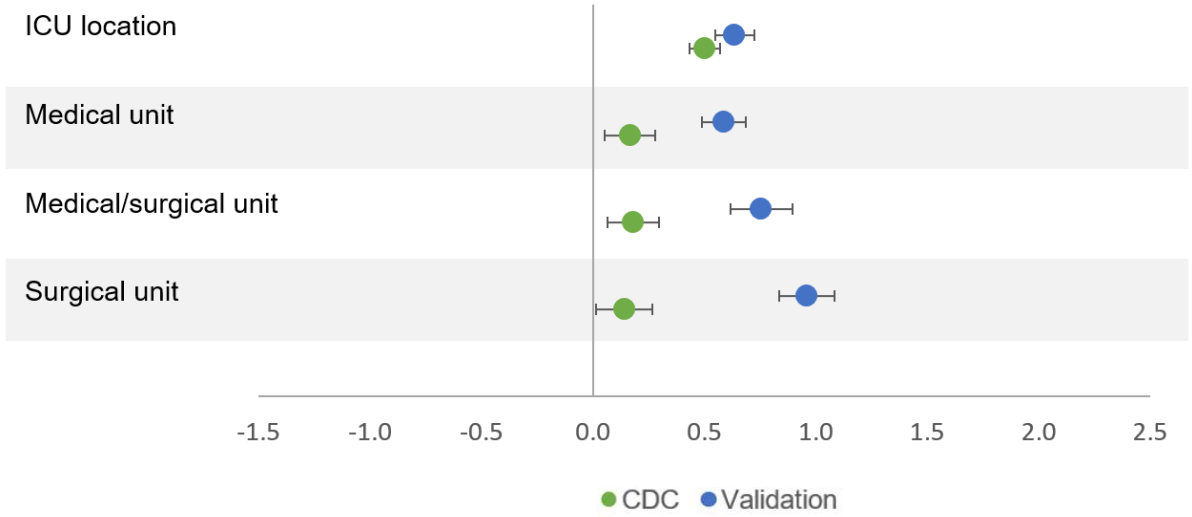


Figure 3.5: Comparison of coefficient estimates for CDC and Validation models for all antibiotic agents



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Chapter 4: Predicting Antibacterial Agent Use for Resistant Gram-Positive Infections in a Nationwide Network of Hospitals

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4.1 Abstract

Background: Antibiotic use metrics are utilized by antimicrobial stewardship programs to benchmark performance against peer institutions and inform stewardship efforts. Benchmarking requires risk-adjustment for patient- and facility-level factors so that remaining differences are attributable only to non-modifiable factors, such as prescribing practices. Antibiotics for the treatment of resistant Gram-positive infections are one of the most frequently used drug classes and a target for stewardship programs. Our objective was to identify significant patient- and facility-level predictors of antibiotic use for agents predominantly used for resistant Gram-positive infections in a nationwide network of hospitals.

Methods: We used data from inpatient encounters at facilities participating in the Vizient data repository between January 1, 2016 and December 31, 2016. The outcome, use of antibacterial agents predominantly used for resistant Gram-positive infections, was calculated as days of therapy (DOT) per patient days present for each encounter. We constructed two models: a multivariable generalized estimating equation (GEE) negative binomial model and a zero-inflated negative binomial model. We assessed the following predictors for inclusion: age, sex, race, ethnicity, diagnosis related groups (DRGs), comorbidities, ICD-10 codes specific to methicillin-resistant *Staphylococcus aureus* (MRSA) infection, days in the intensive care unit (ICU), season of admission, facility bed size, facility teaching status, and region. A clinical framework was used to categorize DRGs based on risk of receiving a Gram-positive agent. We evaluated the association between agents used for resistant

Gram-positive infections and the predictors and compared observed-to-predicted DOT for each model.

Results: 137 facilities representing 3,067,202 encounters met inclusion criteria. All predictors considered in our model were significant. Predictors with the greatest magnitude of association included DRG categories, presence of MRSA ICD-10 code, and length of stay in the ICU. The DRG categories with the greatest association were categories for infections likely due to *Staphylococcus aureus* (RR=7.48; 95% CI 7.24, 7.72), infections requiring long-term treatment (RR=6.31; 95%CI 6.13, 6.50), and infections requiring empiric coverage (RR=3.92; 95% CI 3.86, 3.99). The GEE negative binomial model consistently overpredicted DOT compared to observed DOT for each facility. In contrast, the zero-inflated negative binomial model had improved prediction of DOT.

Conclusions: Diagnosis codes and other patient-level characteristics can be utilized to account for variability in antibiotic use beyond what is explained through facility-level characteristics. Incorporation of the significant predictors identified in this study may aid in more meaningful inter-hospital comparisons of use of agents predominantly used for resistant Gram-positive infections.

4.2 Introduction

Excessive and inappropriate antibiotic use in hospitalized patients is a significant, and modifiable, driver of antibiotic resistance.[1-3] However, hospitals continue to overuse antibiotics[4-6] and antimicrobial stewardship programs (ASPs) have developed to promote judicious antibiotic use in the acute care setting.[7] To

assist ASPs in targeting interventions, the Centers for Disease Control and Prevention (CDC) are encouraging facilities to electronically submit antimicrobial use data through the Antimicrobial Use and Resistance (AUR) module. However the most appropriate metric for comparing antibiotic use between hospitals remains a topic of debate.[8,9]

The current metric for benchmarking hospital performance is the CDC National Healthcare and Safety Network (NHSN) Standardized Antimicrobial Administration Ratio (SAAR). The SAAR metric is based on hospital medication administration data reported to the National Healthcare and Safety Network (NHSN), and is calculated as a ratio of observed-to-predicted antimicrobial use.[10] Predicted use is derived through regression-based indirect standardization using regression models developed by the CDC based on antibiotic administration data from 449 hospitals.[11,12] There are currently six adult SAAR metrics corresponding to different categories of antibiotics: 1) antibacterial agents predominantly used for resistant Gram-positive infections; 2) broad-spectrum antibacterial agents predominantly used for community-acquired infections; 3) broad-spectrum antibacterial agents predominantly used for hospital-onset infections; 4) narrow-spectrum beta-lactam agents; 5) antibacterial agents posing the highest risk for *Clostridioides difficile* infection; and 6) all antibacterial agents.

Because comparisons of antibiotic use between different hospitals are complicated by differences in underlying patient and hospital characteristics, risk-adjustment is necessary for unbiased benchmarking of hospital performance. However, the current SAAR models adjust only for a limited set of facility

characteristics and do not take into account important patient-level characteristics that are known predictors of antibiotic use, such as infections, comorbidities, and length of stay in the ICU. These characteristics influence antibiotic prescribing and known variations in these characteristics exist between hospitals,[13] however it is unknown if the addition of a broader set of covariates will improve risk-adjustment.

The objective of our study was to identify significant patient- and facility-level predictors of antibiotic use for agents predominantly used for resistant Gram-positive infections in a nationwide network of hospitals. We focused on this antibiotic category because it includes vancomycin, one of the most common targets for antimicrobial stewardship efforts. We hypothesized that the addition of new patient- and facility-level predictors would improve risk-adjustment compared to the current CDC SAAR model. Using retrospective cross-sectional data, we developed revised antibiotic utilization prediction models for antibacterial agents predominantly used for resistant Gram-positive infections.

4.3 Methods

4.3.1 Study design and population

We conducted a cross-sectional study using a retrospective dataset of nationwide medical centers containing data on adult and pediatric inpatient encounters. Data were from Vizient, Inc., the largest member owned healthcare company in the US. Vizient serves more than half of the health care organizations across the nation; 50% of the nation's acute care providers and 95% of academic medical centers are Vizient members.[14]

4.3.2 Inclusion and exclusion criteria

All adult patients (≥18 years) with an inpatient hospital encounter between January 1, 2016 and December 31, 2016 were included. For patients who had more than one hospital encounter, each encounter was included. Facilities without antibiotic use data reported for all 12 months of 2016 and/or incomplete reporting of ICU days were excluded.

4.3.3 Data source

We used data from inpatient encounters at facilities contributing pharmacy data to the Vizient Clinical DataBase and Resource Manager (CDB/RM™). The CDB/RM™ is a comparative database used by member hospitals to evaluate both internal and network performance, and as a tool to benchmark against peer hospitals to improve performance.[14] The CDB/RM™ contains procedure- and diagnosis-specific data from charge transaction masters and inpatient billing files. In addition, the database also contains encounter-level data on demographics, diagnoses, procedures, and laboratory results for each hospital discharge.

4.3.4 Risk-adjustment covariates

We considered both facility- and patient-level predictors for inclusion in the risk-adjustment models. Facility-level covariates included teaching status (defined as membership to the Association of American Medical Colleges Council of Teaching Hospitals and Health Systems), hospital bed size, and geographic region. Patient-level covariates included patient age, sex, race, ethnicity, season of admission, ICU days, comorbidities (defined per AHRQ Elixhauser Comorbidity

Software[15]), MRSA-specific ICD-10 codes (A4102, A4902, B9562, J15212), and diagnosis-related groups (DRGs). We did not use the Elixhauser comorbidity score but utilized the framework to identify comorbidities. We used a clinical framework to categorize DRGs based on risk of receiving a Gram-positive agent; categories were informed by pathogen and organ system infected, as well as typical duration of treatment. The framework resulted in 20 distinct DRG categories; four of which were specific to *Staphylococcus aureus* infections. Infection-specific categories and associated DRG codes are provided in Table 4.1. Details for all DRG categorizations are provided in Appendix B.

4.3.5 Antibiotic use outcome

The outcome, use of antibacterial agents predominantly used for resistant Gram-positive infections, was calculated as days of therapy (DOT) per days present for each encounter. Agents for resistant Gram-positive infections were defined per the NHSN antibiotic grouping, and included ceftaroline, dalbavancin, daptomycin, linezolid, oritavancin, quinupristin/dalfopristin, tedizolid, telavancin, and vancomycin (intravenous).[11] This metric is analogous to the NHSN antibiotic use metric, antimicrobial days.[16] One day of therapy was defined as any amount of a Gram-positive agent administered in a calendar day to a patient as documented in the CDB/RM^{TM}. For each encounter, DOT for each Gram-positive agent (the numerator) were summed. If more than one Gram-positive agent was received during an encounter, including more than one agent on the same day, the DOT for each agent were aggregated for total Gram-positive DOT. Days present

(the denominator) was defined as the length of stay for each encounter and was calculated based on admission date.

4.3.6 Variable Selection

Due to the large sample size of data available through the CDB/RM™ data repository, and thus high statistical power, we leveraged a machine learning method to determine the variables that were most important in predicting DOT. To perform variable selection, we used Least Absolute Shrinkage and Selection Operator (LASSO) using the R package, GLMNET.[17] We tuned the lambda parameter and determined that the optimum lambda value was 0.008206. This value resulted in a cross-validation error 5% above the minimum cross-validation error, with minimal impact on test MSE (additional details provided in Appendix B). The LASSO approach was used in the GEE negative binomial model for variable selection, and the selected variables were used in both GEE negative binomial and zero-inflated negative binomial models.

In addition, we ran a full GEE negative binomial model with all potential candidate predictors, and any predictor that had been eliminated by LASSO but had a relative risk ≥2.0 or ≤0.5 was forced into the model. Finally, we checked for collinearity among the independent variables. Where two variables had a correlation coefficient greater than 0.80, we selected one of the two. Correlation of this magnitude occurred where variables were representing the same construct (e.g. ICD-10 code for solid tumor and solid tumor DRG group).

4.3.7 Model construction

Gram-positive DOT for each encounter were aggregated to the facility-level as DOT per 1,000 days present. Antibiotic use data in the CDB/RM^{TM} exhibited overdispersion; as such we constructed a negative binomial regression model to evaluate predictors of antibacterial agents predominantly used for resistant Gram-positive infections. We assessed the correlation structure of our data and because correlation was identified (exchangeable working correlation=0.14), we used a negative binomial, generalized estimating equation (GEE) model. All variables retained via the LASSO algorithm were entered into the model and we used the Wald test to evaluate predictor effect size and significance ($p<0.05$). Due to the high frequency of zero values for our outcome variable (i.e. many patients did not receive any of the included antimicrobial agents), we also constructed a zero-inflated negative binomial regression model to compare predictions with those generated from the GEE negative binomial model. Where p-values or confidence intervals are reported, they are two-sided at the 95% confidence level. All analyses were performed using SAS® software version 9.4[18] and the final models were constructed using the genmod procedure.

4.4 Results

Of 158 facilities with pharmacy data in the CDB/RM^{TM}, 137 had complete reporting of use of antibacterial agents for resistant Gram-positive infections and ICU days across all 12 months of 2016 and were included in our study. The cohort included 3,067,202 inpatient encounters between January 1st, 2016 and December

31st, 2016, representing 16,811,855 total patient days (median number of patient days among facilities=109,530; IQR=48,310-168,997 patient days). There were 2,335,156 total DOT for agents used for resistant Gram-positive infections (median=15,390 DOT; IQR=5,670-25,567 DOT). Approximately 65% of facilities were teaching hospitals, 70% had a hospital bed size greater than 500, and approximately 40% were located in the Midwestern region (Table 4.2).

Out of 79 candidate variables, the LASSO algorithm selected 26 variables for retention in the final models. One additional variable, bone marrow transplant DRG, was eliminated by LASSO but was forced into the GEE negative binomial and zero-inflated negative binomial models based on a relative risk ≥2.0 in the full model. The final models therefore included 27 covariates for risk-adjustment (Table 4.3).

All 27 predictors considered in the final GEE negative binomial model were significant. Predictors with the greatest magnitude of association were DRG categories, followed by presence of an ICD-10 code for MRSA infection, and ICU days and (Table 4.3). DRG categories with the greatest association were the categories for infections likely due to *Staphylococcus aureus* (RR=7.48; 95% CI 7.24, 7.72), infections requiring long-term treatment (RR=6.31; 95%CI 6.13, 6.50), and infections requiring empiric *Staphylococcus aureus* coverage (RR=3.92; 95% CI 3.86, 3.99). Presence of an ICD-10 code for MRSA infection had a large magnitude of association (RR=3.31; 95% CI 3.23, 3.39). Finally, magnitude of association increased as number of days in the ICU increased, with length of stay ≥14 days having the greatest effect (RR=1.89; 95% CI 1.84, 1.94).

As with the GEE negative binomial model, all predictors considered in the zero-inflated negative binomial model were significant, though coefficient estimates were smaller and often negative (Table 4.4). Similar to the DRG predictors in the NB model, the DRGs for infection were also the greatest in magnitude. Coefficient estimates for other significant predictors are shown in Table 4.4. As shown in Figure 4.1a, the GEE negative binomial model consistently overpredicted DOT compared to observed DOT for each facility. In contrast, the zero-inflated negative binomial model had improved prediction of DOT (Figure 4.1b).

4.5 Discussion

Using a large, nationwide cohort of academic and community hospitals, we constructed two different encounter-level models to predict use of antibacterial agents predominantly used for resistant Gram-positive infections. We identified DRGs, MRSA-specific ICD-10 codes, and length of stay in the ICU as the most significant predictors of DOT. Specifically, DRG codes for infections highly likely due to *Staphylococcus aureus* (e.g. cellulitis), infections requiring long term treatment (e.g. osteomyelitis, endocarditis), and infections requiring empiric *Staphylococcus aur*eus coverage (e.g. septicemia, viral meningitis) had the greatest associations.

Of significance is that our primary variable selection procedure, LASSO, eliminated all facility-level predictors from the encounter-level models, lending support to the emerging evidence that patient-level factors are more important in

the prediction of antibiotic use. In addition, when we ran the full negative binomial GEE model with all candidate predictors, facility-level predictors did not meet our criteria for strength of association (RR>=2.0 or ≤0.5) in order to be forced into the model. This is notable because the current CDC SAAR metrics include only facility-level predictors in risk-adjustment.

Our findings suggest that patient characteristics may explain variability in use of agents used for resistant Gram-positive infections beyond that of facility factors. This corroborates previous work investigating patient-level predictors of antibiotic use. Polk et al investigated benchmarking risk-adjusted antibiotic use in 70 hospitals nationwide and found clinical service line (designated based on DRG) to be an important predictor of expected DOT.[9] More recently, in a retrospective cohort of 2.7 million encounters at 35 Kaiser facilities in California, Yu et al reported that DRGs, infection present on admission, and patient class were significant predictors of DOT.[19] Researchers compared a full model ("complex ratio") to a simplified model ("ASP ratio") and found high correlation between models. They observed lower correlation with the facility-level model. In their simplified model for agents predominantly used for resistant Gram-positive infections, DRGs were the strongest predictors, followed by infection present on admission. This is directly in line with findings from our study.

As with previous work, we observed diagnoses to be significant predictors of antibiotic use, however the methods in which DRGs were used for risk-adjustment differed across studies. Yu et al used recursive partitioning to group DRG codes into 4 groups. Polk et al used DRGs to assign patients to one of 35

clinical service lines. Because our study was focused on agents predominantly used for resistant Gram-positive infections, our approach utilized a clinical framework to categorize DRGs into 20 groups based on risk of receiving one of these agents. Despite differences in methods used to incorporate DRGs into risk-adjustment, evidence is accumulating that this specific patient-level factor is important in predicting DOT. We suspect that use of diagnoses in risk-adjustment may vary by antibiotic class and future work should explore the optimal way to model this predictor.

Compared to Yu et al, who included data from Kaiser Permanente Northern and Southern California only, our study sample is comprised of a different patient population. The CDB/RM^{TM} contains data from hospitals nationwide, including large academic medical centers. As such, patients included in our prediction models are expected to be more heterogeneous and thus more representative of the underlying population used to generate the CDC SAAR metrics.

Our GEE negative binomial model consistently overpredicted DOT compared to observed DOT for each facility. This overestimation would bias the SAAR away from the null. However, the overprediction of DOT was non-differential across facilities because DOT were greater than expected for each of the 137 facilities, thus the ratio would be biased for all facilities. Possible reasons for this overprediction include the considerable number of zeros in our dataset (70% of encounters in our study sample did not include a single DOT for agents predominantly used for resistant Gram-positive infections). This makes modeling this outcome at the encounter-level challenging because the number of zeros in

the data is greater than what is allowed by the negative binomial distribution. In addition to excess zeros, we observed clustering at the facility level. It is possible that predicting this outcome at an encounter-level is not easily feasible without a more complex, and less interpretable, modeling approach.

To explore this, we constructed a zero-inflated negative binomial model and found that predicted DOT were much more closely aligned with observed DOT. However, some significant predictors in the GEE negative binomial model had coefficient estimates that changed direction in the zero-inflated model (e.g. the coefficient for ICU days changed from positive to negative), making interpretation of the model complex. Our goal was to construct a model that accurately predicts DOT that clinicians and the stewardship practice community believe adequately risk-adjusts for the types of patients they treat. As such, the zero-inflated negative binomial model may provide better risk-adjustment, but at the expense of interpretability. Yu et al did not report data on predicted versus observed DOT from the Kaiser models; therefore we are unable to compare model performance.

There are limitations to our study. First, the CDB/RM^{TM} data repository contains billing data, not electronic medication administration record or bar-coded medication administration data as in the NHSN. This likely would have resulted in an overestimate of antibiotic use in the CDB/RM^{TM}, however we would expect similar overestimation across all included facilities. In addition, we did not have data on culture results which may have improved the prediction of DOT. Finally, our data are restricted to a single calendar year. Including data from multiple years in the models would allow us to assess the stability of predictors over time.

In conclusion, this study supports previous work that patient-level characteristics may explain variability of inpatient antibiotic use beyond what is explained by facility-level factors, specifically for agents predominantly used for resistant Gram-positive infections. Future work is needed to explore whether these same predictors hold for additional antibacterial groupings. Additional work is also needed to investigate the optimal modeling approach for encounter-level datasets. It is essential that risk-adjusted antibiotic use metrics are optimized in order to ensure the validity of ranking hospitals based on antibiotic use. In the near future, antimicrobial utilization data may be used to judge hospital performance and as a pay-for-performance outcome; as such, further research on risk-adjustment methodology is warranted.

Tables and Figures

Table 4.1. Infection-specific diagnosis-related group (DRG) categories

DRG Name	DRG Code(s)
Infections requiring empiric MRSA coverage	
Bacterial & Tuberculosis Infections of Nervous System	94, 95, 96
Non-Bacterial Infections of Nervous System	98, 99
Acute Major Eye Infections	121, 122
Respiratory Infections and Inflammations	177, 178, 179
Pleural Effusion	186, 187, 188
Simple Pneumonia & Pleurisy	193, 194, 195
Fever	864
Septicemia or Severe Sepsis	870, 871, 872
Viral Meningitis	75, 76
Infections highly likely due to *Staphylococcus aureus*	
Septic Arthritis	548, 549, 550
Skin Graft for Skin Ulcer or Cellulitis	573, 574, 575
Skin Graft except for Skin Ulcer or Cellulitis	576, 577, 578
Cellulitis	602, 603
Infections likely to require long term MRSA coverage	
Acute & Sub-acute Endocarditis	288, 289, 290
Osteomyelitis	539, 540, 541
Infections not likely due to *Staphylococcus aureus*	
Otitis Media & URI	152, 153
Bronchitis & Asthma	202, 203
Major Gastrointestinal Disorders & Peritoneal Infections	371, 372, 373
Knee Procedures With Prior Diagnosis of Infection	485, 486, 487
Kidney, Urinary Tract, & Female Reproductive System Infections	689, 690, 757, 758, 759
Infectious & Parasitic Diseases With OR Procedure	853, 854, 855
Post-operative and/or Post-Traumatic Infections with or without OR Procedure	856, 857, 858, 862, 863
Viral Illness	865, 866
Other Infectious & Parasitic Diseases Diagnoses	867, 868, 869

Abbreviations: DRG: diagnosis-related group; MRSA: Methicillin-resistant *Staphylococcus aureus*; OR: operating room; URI: upper respiratory infection

Table 4.2. Characteristics of included hospitals (N=137)

Characteristic	Vizient hospitals (n (%))
Region	
New England/Mid-Atlantic	46 (33.6)
Southeast	21 (15.3)
Midwest/Mid-Continent	54 (39.4)
West	16 (11.7)
Teaching hospital[a]	90 (65.7)
Bed size	
1-249	31 (22.6)
250-499	27 (19.7)
500-749	40 (29.2)
750+	30 (21.9)
Unknown	9 (6.6)
Level 1 Trauma Center[b]	62 (72.9)
Transplant service[c]	56 (40.9)
Case Mix Index[d]	
0-1.49	15 (10.9)
1.5-1.99	49 (35.8)
2.0+	73 (53.3)

[a]Teaching status based on Association of American Medical Colleges Council of Teaching Hospitals and Health Systems membership

[b]Level defined per the American Trauma Society

[c]Facility has a transplant service if it performs one or more of the following transplants: heart, lung, heart/lung, intestinal, kidney, liver, pancreas

[d]Calculated as average Diagnosis Related Group (DRG) weight; magnitude of weight related to average resource demand per DRG

Table 4.3. Significant predictors of days of therapy for antibacterial agents used for resistant Gram-positive infections

Predictor	Relative Risk (95% CI)
Diagnosis-Related Group (DRG category)*	
Infection likely Staphylococcus	7.48 (7.24, 7.72)
Infection requiring long-term treatment	6.31 (6.13, 6.50)
Infection requiring empiric Staphylococcus coverage	3.92 (3.86, 3.99)
Infection not Staphylococcus	3.11 (3.05, 3.18)
Orthopedic surgery	2.63 (2.45, 2.83)
Neurosurgery	2.35 (2.24, 2.47)
Other surgery	2.19 (2.15, 2.24)
Invasive life support	1.70 (1.65, 1.75)
Implantable device	1.97 (1.89, 2.05)
Bone marrow transplant	2.19 (1.80, 2.66)
Obstetric surgery	0.43 (0.41, 0.44)
MRSA ICD-10 code	3.31 (3.23, 3.39)
ICU days	
1 day in ICU	1.31 (1.27, 1.35)
2-3 days in ICU	1.34 (1.31, 1.37)
4-7 days in ICU	1.55 (1.51, 1.58)
8-13 days in ICU	1.73 (1.69, 1.77)
14+ days in ICU	1.89 (1.84, 1.94)
Age group	
Age 30-64	1.22 (1.21, 1.24)
Age 65-79	1.15 (1.12, 1.17)
Age 80+	0.94 (0.92, 0.96)
Male	1.21 (1.20, 1.22)
Comorbidities	
Deficiency anemias	1.15 (1.14, 1.16)
Weight loss	1.16 (1.15, 1.17)
Fluid Disorders	1.11 (1.10, 1.12)
Lymphoma	1.57 (1.54, 1.60)
Hypertension	1.04 (1.03, 1.05)
Diabetes mellitus	1.11 (1.10, 1.11)

Abbreviations: DRG: diagnosis-related group; ICD-10: International Classification of Diseases, Tenth Revision; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*

*A clinical framework was used to categorize DRGs based on risk of receiving a Gram-positive antibacterial agent

Table 4.4. Coefficient estimates for significant predictors of days of therapy for antibacterial agents used for resistant Gram-positive infections, by model type

Predictor	GEE NB Model Estimate (95% CI)	Zero-inflated NB model Estimate (95% CI)	
		Count process	Zero process (logistic)
Diagnosis-Related Group (DRG category)*			
Infection likely Staphylococcus	2.01 (1.98, 2.04)	0.61 (0.60, 0.62)	-4.15 (-4.23, -4.06)
Infection requiring long-term treatment	1.84 (1.81, 1.87)	0.61 (0.58, 0.64)	-3.52 (-3.67, -3.36)
Infection requiring empiric Staphylococcus coverage	1.37 (1.35, 1.38)	0.39 (0.38, 0.40)	-2.44 (-2.46, -2.42)
Infection not Staphylococcus	1.14 (1.11, 1.16)	0.37 (0.36, 0.38)	-1.69 (-1.71, -1.67)
Orthopedic surgery	0.97 (0.90, 1.04)	-0.31 (-0.32, -0.30)	-2.54 (-2.58, -2.51)
Neurosurgery	0.85 (0.81, 0.90)	-0.56 (-0.57, -0.54)	-4.83 (-5.05, -4.62)
Other surgery	0.79 (0.76, 0.81)	0.21 (0.19, 0.22)	-1.14 (-1.16, -1.12)
Invasive life support	0.53 (0.50, 0.56)	0.11 (0.10, 0.13)	-0.92 (-0.95, -0.88)
Implantable device	0.68 (0.63, 0.72)	-0.02 (-0.04, -0.003)	-1.34 (-1.38, -1.31)
Bone marrow transplant	0.78 (0.59, 0.98)	-0.04 (-0.07, -0.004)	-1.92 (-2.01, -1.83)
Obstetric surgery	-0.85 (-0.88, -0.81)	-0.10 (-0.14, -0.06)	1.25 (1.20, 1.29)
MRSA ICD-10 code	1.20 (1.17, 1.22)	0.69 (0.67, 0.70)	-4.71 (-5.05, -4.36)
ICU days			
1 day in ICU	0.27 (0.24, 0.30)	-0.28 (-0.29, -0.27)	-1.14 (-1.16, -1.12)
2-3 days in ICU	0.29 (0.27, 0.31)	-0.25 (-0.26, -0.24)	-1.24 (-1.26, -1.23)
4-7 days in ICU	0.44 (0.41, 0.46)	-0.24 (-0.25, -0.23)	-1.70 (-1.73, -1.68)
8-13 days in ICU	0.55 (0.53, 0.57)	-0.22 (-0.23, -0.21)	-2.13 (-2.16, -2.09)
14+ days in ICU	0.63 (0.61, 0.66)	-0.23 (-0.24, -0.22)	-2.81 (-2.86, -2.77)
Age group			
Age 30-64	0.20 (0.19, 0.21)	-0.09 (-0.10, -0.08)	-0.46 (-0.48, -0.45)
Age 65-79	0.14 (0.12, 0.15)	-0.22 (-0.23, -0.21)	-0.54 (-0.56, -0.52)
Age 80+	-0.06 (-0.08, -0.04)	-0.38 (-0.39, -0.36)	-0.33 (-0.35, -0.31)
Male	0.19 (0.18, 0.20)	0.04 (0.04, 0.05)	-0.31 (-0.32, -0.29)
Comorbidities			

Deficiency anemias	0.14 (0.13, 0.15)	-0.05 (-0.05, -0.04)	-0.44 (-0.46, -0.43)
Weight loss	0.15 (0.14, 0.16)	0.05 (0.04, 0.05)	-0.31 (-0.32, -0.28)
Fluid Disorders	0.11 (0.10, 0.12)	-0.04 (-0.04, -0.03)	-0.29 (-0.31, -0.28)
Lymphoma	0.45 (0.43, 0.47)	0.10 (0.08, 0.12)	-0.85 (-0.89, -0.81)
Hypertension	0.04 (0.03, 0.05)	0.05 (0.04, 0.05)	0.01 (-0.0002, 0.02)
Diabetes mellitus	0.10 (0.09, 0.11)	-0.02 (-0.03, -0.02)	-0.27 (-0.28, -0.26)

Abbreviations: DRG: diagnosis-related group; GEE: generalized estimating equation; ICD-10: International Classification of Diseases, Tenth Revision; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*; NB: negative binomial

*A clinical framework was used to categorize DRGs based on risk of receiving a Gram-positive antibacterial agent

Figure 4.1a. Negative binomial GEE regression model: comparison of observed and predicted DOT for agents predominantly used for resistant Gram-positive infections, by facility

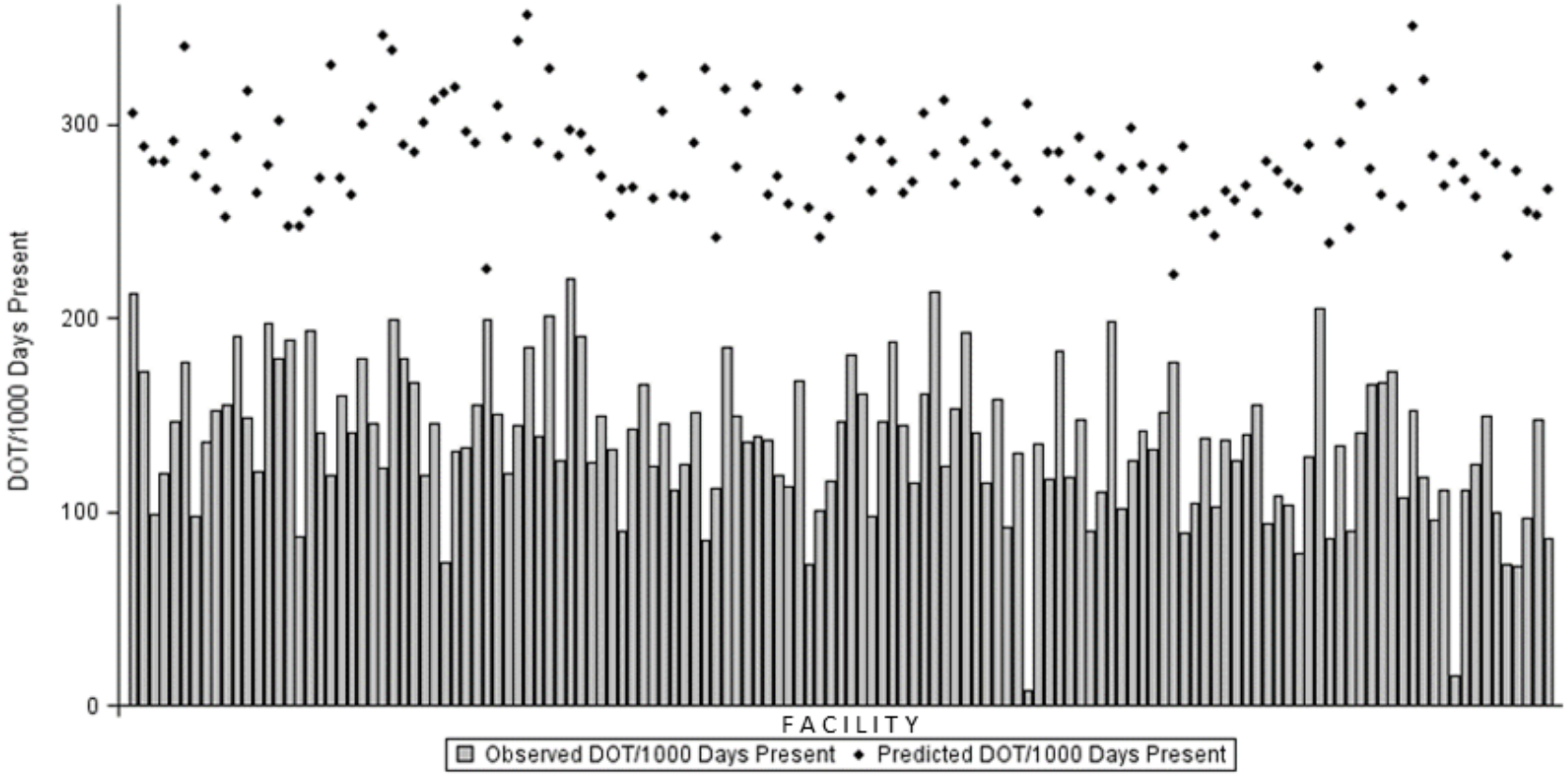
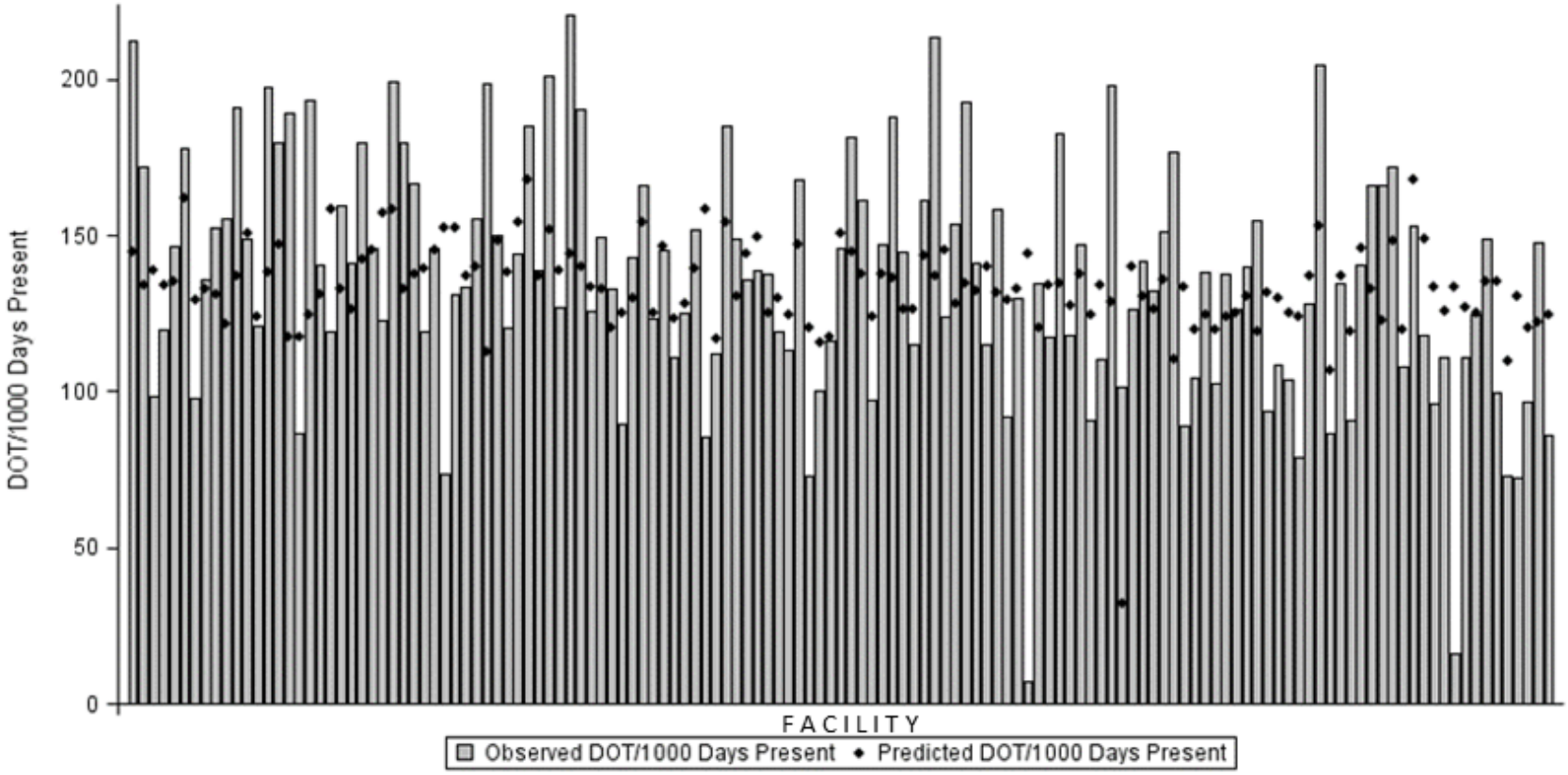


Figure 4.1b. Zero-inflated negative binomial regression model: comparison of observed and predicted DOT for agents predominantly used for resistant Gram-positive infections, by facility



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Chapter 5: Risk-adjusted Total Antibiotic Use versus Appropriate Antibiotic Use for Antibacterial Agents Predominantly Used for Resistant Gram-Positive Infections

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5.1 Abstract

Background: Judicious antibiotic use is essential to limit the spread of antibiotic-resistant bacteria and improve the health and safety of both the individual patient and the population. The Centers for Disease Control and Prevention (CDC) has developed a risk-adjusted metric, the Standardized Antimicrobial Administration Ratio (SAAR), which hospitals may use to benchmark performance against peer facilities. However, there are no data to indicate if risk-adjusted antibiotic use adequately accounts for indication for use. Our objective was to test whether the SAAR, a risk-adjusted metric of total antibiotic utilization, is a scientifically valid proxy measure for appropriate antibiotic use for antibacterial agents predominantly used for resistant Gram-positive infections.

Methods: We conducted a retrospective, cross-sectional study using data from patients admitted to Oregon Health & Science University (OHSU) Hospital between July 31, 2017 and August 1, 2018 and who received a Gram-positive antibiotic agent. To calculate the SAAR metric, all adult patients were included. To calculate the proportion of appropriate use, patients must have received at least one administration of a Gram-positive agent (ceftaroline, dalbavancin, daptomycin, linezolid, oritavancin, quinupristin/dalfopristin, tedizolid, telavancin, or intravenous vancomycin) in a CDC-defined SAAR location type (medical intensive care unit (ICU), medical-surgical ICU, surgical ICU, medical ward, medical-surgical ward, surgical ward, general hematology-oncology, step-down). We identified patients and assessed antibiotic appropriateness using both a data repository containing electronic health record data and manual chart review.

We generated two outcomes of Gram-positive antibiotic use: SAAR and proportion of appropriate use. To calculate SAAR, predicted days of therapy (DOT) was derived

using coefficients from the 2017 CDC regression model. The proportion of appropriate use was based on an automated classification tool and chart-review informed assessments and was calculated as appropriate DOT out of total DOT. We ranked each calendar month of OHSU performance by SAAR and proportion of appropriate use from highest to lowest, and used Spearman Rank Correlation to assess correlation between SAAR and proportion of appropriate use. Qualitatively, a difference in three or more rankings between the two measures was considered meaningful.

Results: A total of 1,621 encounters, representing 1,430 patients were included. There were 2,235 antibiotic courses administered, totaling 7,721 DOT. Per the classification rubric, 773 encounters (48%) had courses that were automated appropriate; 848 encounters required chart review. Across the 12 month study period, the average SAAR value was 1.07 (range 0.88-1.34); the average proportion of appropriate use was 0.96 (range 0.92-0.99). Compared to the SAAR ranking, more than half of months changed rank by three or more positions. There was minimum correlation between measures (Rho=0.22; 95% CI -0.41, 0.70).

Conclusions: In our study where appropriate antibiotic use was high, risk-adjusted total use was not a valid proxy for appropriate use. This finding is based upon one year of data from a single facility and for a single antibiotic grouping: agents for resistant Gram-positive infections. Future work should assess if these findings are generalizable beyond OHSU and consistent across other antibiotic classes.

5.2 Introduction

Judicious antibiotic use is essential to combat the global public health crisis of antibiotic resistance and to improve the health and safety of patients. In the United States alone, the Centers for Disease Control and Prevention (CDC) report that there are over 2 million infections and 23,000 deaths cause by antibiotic-resistant bacteria each year.[1] A critical component in combating antibiotic resistance in the inpatient setting is the antimicrobial stewardship program (ASP).

Effective ASPs should be actively engaged in tracking antibiotic use data within facilities,[2] and the CDC has recently developed the Standardized Antimicrobial Administration Ratio (SAAR) as a metric to assist ASPs in measuring and evaluating antimicrobial use at the facility level.[3] However, the most appropriate metric for comparing antibiotic use across hospitals remains a topic of debate.[4] In addition, like healthcare-associated infections where the goal is zero infections, improving antibiotic use also requires a target. In antimicrobial stewardship, though, there is currently no clear target for expected antibiotic use.

The SAAR metric is calculated as a ratio of observed-to-predicted antibiotic use, with predicted use derived through regression-based indirect standardization.[3] There are currently six different adult SAAR metrics that have been developed for categories of antibiotics: 1) antibacterial agents predominantly used for resistant Gram-positive infections; 2) broad-spectrum antibacterial agents predominantly used for community-acquired infections; 3) broad-spectrum antibacterial agents predominantly used for hospital-onset infections; 4) narrow-spectrum beta-lactam agents; 5) antibacterial agents posing the highest risk for *Clostridioides difficile* infection; and 6) all antibacterial agents.[5]

To ensure that current CDC SAAR metrics based on total antibiotic use are accurately informing stewardship efforts, it is essential to determine if the metrics are a valid proxy for appropriate antibiotic use. Currently, there are no data supporting the validity of the SAAR metric as a proxy for measuring appropriate antibiotic use. If suboptimal antibiotic use metrics are used to guide stewardship strategies, ASPs may design unnecessary or ineffective interventions and, ultimately, hospitals may be inappropriately penalized in benchmarking comparisons with peer hospitals.

The objective of this study was to evaluate the validity of one CDC risk-adjusted antibiotic use metric by assessing correlation with appropriate use as determined by clinical criteria. We hypothesized that in a single healthcare facility over time, the relative performance will differ when evaluated based on the SAAR metric compared to a measure of appropriate antibiotic use.

5.3 Methods

5.3.1 Study design and population

We constructed a retrospective cohort of adult inpatients (≥18 years) admitted to Oregon Health & Science University Hospital (OHSU) between August 1, 2017 and July 31, 2018. OHSU Hospital is a 556-bed academic, quaternary-care facility in Portland, Oregon and 90% of health care patients reside in Oregon.[6]

5.3.2 Inclusion and exclusion criteria

To be included, patients must have received at least one administration of an agent from the CDC SAAR antibiotic grouping for agents predominantly used for resistant Gram-positive infections: ceftaroline, dalbavancin, daptomycin, linezolid, oritavancin,

quinupristin/dalfopristin, tedizolid, telavancin, or vancomycin (intravenous).[7] Patients were identified for inclusion through the Pharmacy Research Repository (PHARR), a research data repository that includes longitudinal electronic health record data for all OHSU patients. A course was defined as no greater than a 27 hour gap in consecutive administrations of an agent, and only courses that were administered in a SAAR location type (medical intensive care unit (ICU), medical-surgical ICU, surgical ICU, medical ward, medical-surgical ward, surgical ward, general hematology-oncology, step-down)[5] were included.

5.3.3 Data collection

Data were collected through two means: the PHARR data repository and manual chart review of electronic health records. Data collected from PHARR included demographics and encounter-level data, including microbiology, laboratory, diagnosis and procedure codes, any surgeries that occurred (including cut and close times), pharmacy, and medication allergies. All data collected via chart review were recorded in REDCap, a HIPAA-compliant web-based electronic data capture software. Repository data were prepopulated in REDCap with relevant data (e.g. surgery time, allergies, microbiology) to reduce time spent manually reviewing charts.

5.3.4 Outcome variable definitions

We generated two antibiotic use measures for each of the 12 months of the study period: one measure for risk-adjusted total antibiotic use (the SAAR metric) and another for proportion of appropriate use. The SAAR metric for agents used for resistant Gram-positive infections was calculated for OHSU hospital following CDC methodology.[3,5,7]

Specifically, the SAAR metric was calculated as the ratio of observed-to-predicted antibiotic use where observed use was days of therapy (DOT) per 1000 days present and predicted use was derived by applying covariate-specific weights (coefficients) to observed days of therapy. The variables used in the CDC SAAR model to predict DOT for agents used for resistant Gram-positive infections were the following: location type (listed above), facility type (critical access, general acute care, oncology, surgical, Veteran's Affairs, military, women's, and women's and children), number of hospital beds (≥66 beds), and average length of stay ≥3.3 days).[5] Additional model details are provided in Appendix C.

Using NHSN guidance for mapping patient care locations,[8] OHSU patients were mapped to the following SAAR location types for risk-adjustment: medical ICU, surgical ICU, medical ward, surgical ward, and general hematology-oncology. Encounter-level DOT were aggregated to the month-level to generate a SAAR value for each month. For the proportion of appropriate use measure, we used a combination of a classification rubric (described below) and manual chart review to assess whether antibiotic use was appropriate. As with the SAAR metric, total DOT and appropriate DOT were calculated at the encounter-level and aggregated to the month-level.

To inform criteria for appropriateness, reviewers used a combination of clinical practice guideline recommendations from professional societies and OHSU internal protocols.[9-13] We defined inappropriate antibiotic use as any case in which there was an opportunity for de-escalation, including discontinuation. We incorporated a time-varying component into the outcome definition due to empiric antibiotic use that was initially appropriate but later deemed inappropriate. For example, if a patient was administered a

5-day course of vancomycin for cellulitis and the culture grew methicillin-susceptible *Staphylococcus aureus* on Day 3, the course would be considered appropriate through Day 3 and inappropriate for Days 4-5. Thus, the proportion of appropriate use measure was calculated at the encounter-course-day level and courses were assessed as either entirely inappropriate, entirely appropriate, or partially appropriate (i.e. appropriate through a specific day). Reasons for inappropriate DOT included the following: 1) only Gram-negative organism, fungus, or yeast identified on culture; 2) narrower-spectrum agent available; 3) longer duration than indicated; or 4) no evidence of infectious process.

To standardize retrospective evaluation of the appropriateness assessments and automate classification for a subset of charts, we constructed a rubric to guide assessments (Figure 5.1). Auto-classification was implemented using pharmacy, culture, and surgical data obtained from the PHARR data repository. As shown in Figure 5.1, automated assessments utilized pharmacy data to first identify surgical prophylaxis and short-course empiric therapy. Second, we used culture source and results to auto-classify specific courses as appropriate. Encounters could be classified as appropriate via more than one algorithm. Automated classifications of appropriateness were coded in SAS, version 9.4[14] and were uploaded to the REDCap data collection tool. Additional details of the rules used to determine appropriateness are provided in Table 5.1. To check for misclassification of courses that were auto-designated as appropriate via the rubric, we manually reviewed a 10% random sample of the electronic medical records to validate the auto-classification.

Antibiotic courses that did not fall within the auto-classification pathways were identified for manual chart review. This allowed for non-discrete data, such as provider

notes, to be incorporated into the assessment of appropriateness. For complex cases in which there was uncertainty about the appropriateness of the treatment regimen, reviewers requested second and third reviews as needed. All assessments flagged for third review were evaluated by an antibiotic stewardship expert panel comprised of OHSU infectious disease physicians and pharmacists. A 5% random sample of all manual chart review assessments were reviewed by the expert panel to calculate overall classification accuracy.

5.3.5 Analytic Approach

To assess the validity of SAAR as a proxy for appropriate use, we conducted both qualitative and quantitative assessments of concordance between the two measures. We first ranked each calendar month of OHSU performance by SAAR and the proportion of appropriate use. We created slopegraphs to compare the ranks of the two measures and the potential impact on benchmarking ranking. A difference in three or more rankings between the two measures was considered meaningful. We tested the null hypothesis that there is no association between the rank orders of monthly SAAR and proportion of appropriate use using Spearman Rank Correlation. All analyses were performed in SAS, version 9.4.[14]

5.4 Results

A total of 1,621 encounters, representing 1,430 patients, met inclusion criteria. The majority of patients were male (59.3%), white (87.9%), and non-Hispanic (94.4%). The median age was 58 years (IQR 46 years–68 years). Nearly two-thirds of patients were admitted from the Emergency Department. There were a total of 23,599 days present,

and the median length of stay was 9 days (IQR=5-17 days). There were 2,235 courses of Gram-positive antibiotics administered during the study period for a total of 7,721 DOT. Over three-quarters of encounters had only one Gram-positive agent administered during the entire encounter, and vancomycin was the most commonly used agent (89.4%), followed by daptomycin (6.3%) and linezolid (3.4%). Additional encounter characteristics are provided in Table 5.2.

Per the classification rubric, 773 courses (47.7%) were automated as appropriate. Of these, 433 courses (56.0%) were appropriate per 24-hour empiric vancomycin (no culture) algorithm, 329 courses (42.6%) were appropriate per 48-hour empiric coverage with no growth or negative culture algorithm, 209 courses (27.0%) were appropriate per the organism-drug match algorithm, and 32 courses (4.1%) were appropriate per surgical prophylaxis. Of the 10% random selection of automated assessments sampled for validation of the rubric, 100% of courses were accurately classified as appropriate. This left 848 encounters requiring manual chart review. We checked the concordance of our manual assessments with those of the expert panel, and calculated an overall classification accuracy of 87.3%.

Of 1,621 encounters, the vast majority of first courses were classified as entirely appropriate (89.3%), followed by partially appropriate (8.5%), and entirely inappropriate (2.2%). The primary reason for inappropriate DOT was only Gram-negative organism, fungus, or yeast identified on culture (n=89 courses), followed by narrower spectrum agent available (n=56 courses), and no evidence of infectious process (n=14 courses). Of 6,357 first course DOT, 6,116 were classified as appropriate, for an average proportion of appropriate use of 0.96 across the study period. The average SAAR value was 1.07.

Across the 12 months, SAAR values ranged from 0.88 in August to 1.34 in June, while proportion of appropriate use ranged from 0.92 in July to 0.99 in January and September (Table 5.3). Compared to the SAAR ranking, more than half of the months changed rank by three or more positions based on the proportion of appropriate use: three months (January, February, and October) increased by three or more positions; four months (March, April, June, July) decreased by three or more positions, while the remaining five months did not change meaningfully in rank (Figure 5.2). There was minimum correlation between metrics (Rho=0.22; 95% CI: -0.41, 0.70).

5.5 Discussion

In this retrospective, cross-sectional study of inpatients at OHSU hospital during a single year, we found that risk-adjusted antibiotic use is not a valid proxy for appropriate antibiotic use for agents predominantly used for resistant Gram-positive infections. Based on more than half of months changing rank by three or more positions and minimum correlation demonstrated between metrics as assessed via Spearman Rank Correlation, we identified that the relative performance of the hospital over time was meaningfully different based on SAAR versus the proportion of appropriate use. While some fluctuation in months may be expected, we would not expect changes in rank of three or more to occur if total use was correlated with appropriate use.

While numerous studies have investigated the optimal method for risk-adjusted antibiotic use,[15-18] to our knowledge, this is the first study to evaluate the degree to which a risk-adjusted antibiotic utilization metric correlates to appropriate antibiotic utilization. Currently the CDC promotes the use of SAAR for evaluations of antibiotic use within a

single facility by comparing metrics between locations within a hospital and across time. Comparisons between hospitals (benchmarking) requires that facilities share their data for evaluation outside of the NHSN reporting system. As such, our focus on a single facility over time is aligned directly with the most common use of the SAAR metrics.

Antibiotics are essential to effectively treat many hospitalized patients and a certain amount of use is expected; however unnecessary and inappropriate use increases the prevalence of antibiotic resistant infections which are associated with increased patient morbidity and mortality. It is estimated that up to 50% of antibiotics are prescribed sub-optimally, meaning they are either unnecessary or excessively broad spectrum (19, 37, 84).[19-21] Without consideration for indication, the stewardship community is hesitant to incorporate SAAR into practice.[4]

Despite this limitation, there is preliminary work exploring changes in SAAR after implementation of stewardship activities.[22,23] While the goal of the SAAR metric is ultimately to facilitate benchmarking across facilities, it is unknown whether changes in SAAR values are associated with changes in appropriate antibiotic use and ideally patient outcomes. The variables used for risk-adjustment in the development of the SAAR models were limited to facility-level predictors (e.g. hospital bed size and teaching status) and did not include patient-level variables with known face validity as potential predictors of antibiotic use. More importantly, incorporating indication for use is not yet considered. As such, the interpretation of changes in SAAR values in response to a stewardship intervention remains unclear.

Historically, manual review of electronic health records was the primary method for assessing appropriateness of antimicrobial use.[24] However, many variables necessary

to assess appropriate use can be directly extracted from electronic health records, making it possible to automate assessments for a subset of charts based on clinical data alone. This study utilized such an algorithm, reducing chart review burden by nearly 50%. Expanding the algorithm to other drug classes is an important next step in automating classification of appropriateness and supporting efforts to identify targets for stewardship.

There are limitations to our study. First, data were collected from a single institution comprised of a homogeneous patient population over a one year period. In addition, we assessed the validity of total use as a proxy for appropriate use for a single SAAR antibiotic category: agents predominantly used for resistant Gram-positive infections. We focused on this class because these agents are commonly used in hospitalized patients, are a common target for stewardship interventions, and treatment can often be stopped on the basis of culture results. Thus, this antibiotic group was a practical starting point for an investigation comparing risk-adjusted total use versus appropriate use. Finally, there are limitations to data collected via chart review. We attempted to minimize chart review error by using standardized abstraction forms, creating a chart review manual for data abstractors, and piloting a subset of the chart reviews to ensure that reviewers were trained in the methodology. To validate our assessments, we compared a random sample of our classifications with those of an expert panel. We had an overall classification accuracy of 87%, indicating that reviewers performed well when compared to expert assessments as the reference standard.

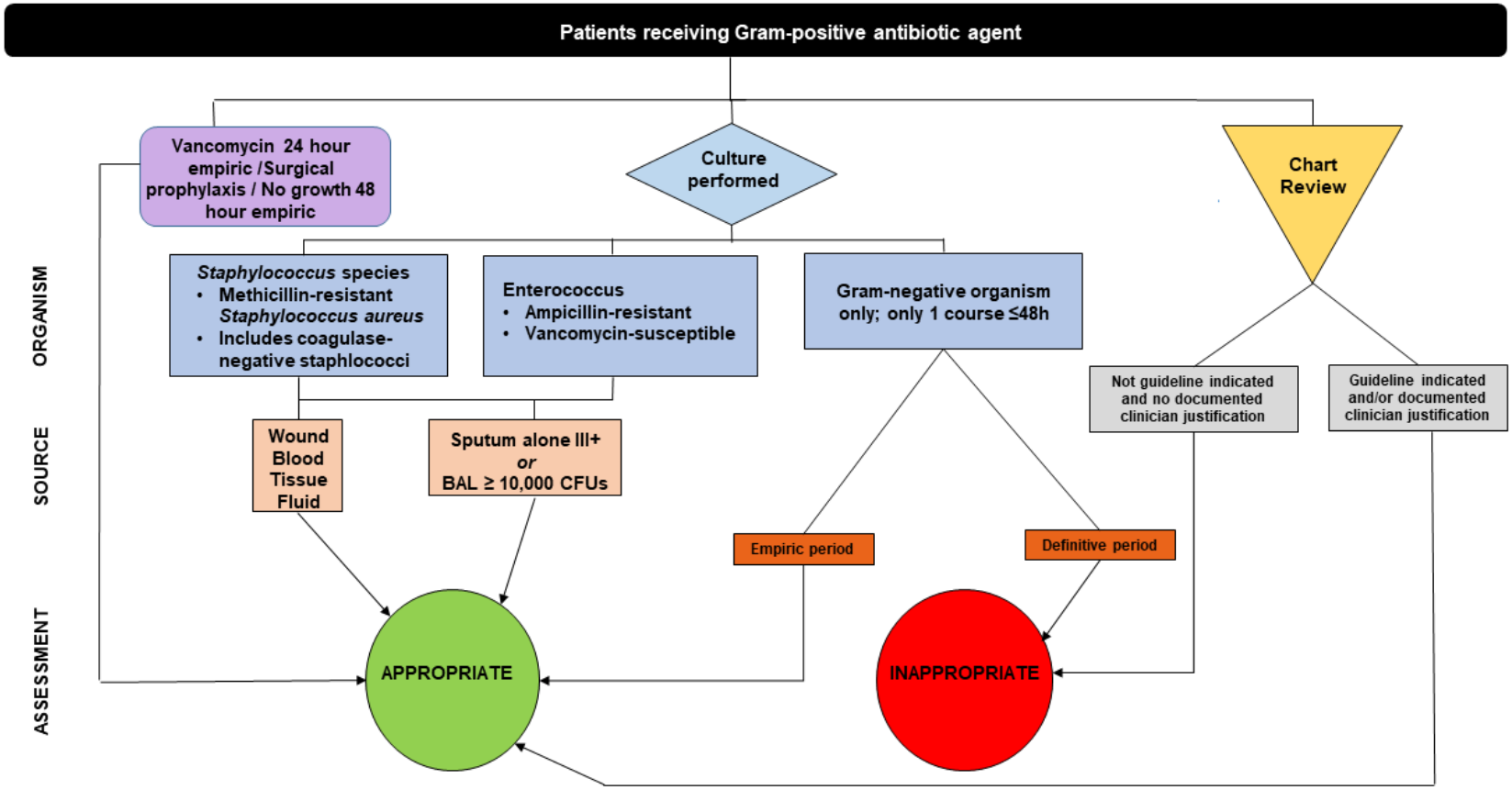
It is important to note that our sample size for assessing correlation between the two measures was small. Also, the proportion of appropriate use measure displayed little variation across months; the measure ranged from 0.92 to 0.99. Despite this narrow

range, more than half of the months had a meaningful change in rank order. It is also worth highlighting that OHSU has a dedicated stewardship team. Overall, during our study period, providers were judicious in their use of Gram-positive agents; it is important to explore the relationship between total antibiotic use and appropriate antibiotic use in settings where there is greater variability in appropriateness.

Future work should explore additional antibacterial categories to determine if our findings are consistent across other SAAR metrics. We suspect that for other groupings, such as broad-spectrum agents predominantly used for hospital-onset infections, the proportion of appropriate use values will be lower as the clinical guidance about when to de-escalate these agents is less straightforward. Also, calculation of SAAR in this study was based on the 2017 CDC SAAR models. The CDC is continually working to update the models, which may impact SAAR performance in the future. Finally, expanding beyond a single institution would increase the external validity of our findings.

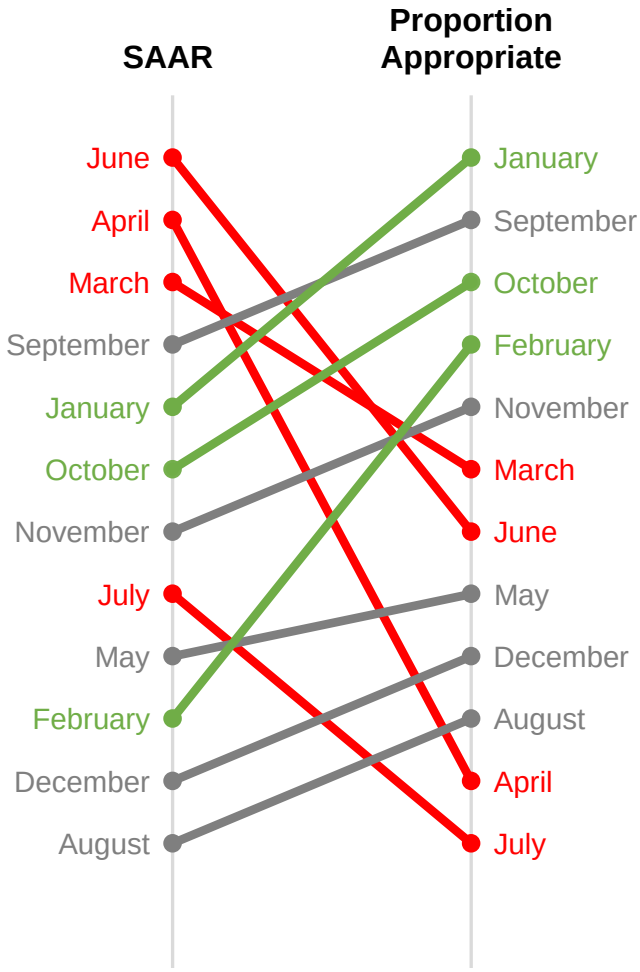
In conclusion, in our study where appropriate antibiotic use was high, risk-adjusted total use was not a valid proxy for appropriate use. With the increasing public health burden of antibiotic resistance and the likelihood of government-mandated stewardship activities in the near future,[25] it is imperative that measures of antibiotic utilization are scientifically valid. While the SAAR metric represents an important step forward for the stewardship community in the effort to combat drug-resistant infections, developing metrics that incorporate indication and expanding electronic assessments of appropriateness are important next steps in improving the quality of antimicrobial prescribing.

Figure 5.1. Classification rubric to identify appropriateness of antibacterial agents predominantly used for resistant Gram-positive infections



Antibiotics defined per National Healthcare Safety Network grouping for agents predominantly used for resistant Gram-positive infections: ceftaroline, dalbavancin, daptomycin, linezolid, oritavancin, quinupristin/dalfopristin, tedizolid, telavancin, vancomycin (intravenous route only)
Abbreviations: BAL: bronchoalveolar lavage; CFUs: colony forming unit

Figure 5.2. Comparison of risk-adjusted antibiotic use (SAAR) and proportion of appropriate use for antibacterial agents predominantly used for resistant Gram-positive infections (Oregon Health & Science University; July 31, 2017-August 1, 2018)



Note: Months are ranked in order from highest to lowest. Months colored green increased in rank by three or more positions, months colored red decreased in rank by 3 or more positions, and months colored grey did not increase or decrease by more 3 or more positions.

Table 5.1. Definitions for automated appropriate classifications

Classification	Definition
≤24 hours empiric vancomycin	• Only 1 course and 1 agent (vancomycin) lasting no more than 24 hours
Surgical prophylaxis	• Agent administered on same day as surgery start time; course ≤24 hours from time of closure; limited to only one course for entire encounter
Culture-related	• Organism-Drug match: Specimen taken day after or on first course start date and sample from wound, blood, tissue, or fluid; appropriate quantity and organism: Staphylococcus (methicillin-resistant) or Enterococcus (ampicillin-resistant and/or vancomycin-susceptible) • Negative culture, empiric therapy: No organisms grew and therapy ≤48 hours • Gram-negative only: Only Gram-negative organism, fungi or yeast identified; only 1 course administered during encounter

Table 5.2. Characteristics of included encounters (N=1,621)

Characteristic	n (%)
Race	
White	1,424 (87.9)
Black	47 (2.9)
Asian	43 (2.7)
American Indian/Alaska Native	28 (1.7)
Other/Unknown	79 (4.9)
Hispanic or Latino	90 (5.6%)
Male	961 (59.3)
Age at admission	
18-29	119 (7.3)
30-64	945 (58.3)
65-79	476 (29.4)
80+	81 (5.0)
Admitted from Emergency Department	1022 (63.1)
Penicillin or cephalosporin allergy	293 (18.1)
MRSA ICD-10 diagnosis	231 (14.3)
Number of courses	
1	1621 (100)
2	275 (17.0)
3 or more	118 (7.3)
One course only during encounter	1228 (76.0)
1st antibiotic course	
Vancomycin	1458 (89.9)
Daptomycin	87 (5.4)
Linezolid	60 (3.7)
Ceftaroline	16 (0.9)

Abbreviations: MRSA: methicillin-resistant *Staphylococcus aureus*

Table 5.3. Raw values for slopegraph rankings for antibacterial agents predominantly used for resistant Gram-positive infections

Month	SAAR	Proportion of Appropriate Use (95% CI)
January	1.08	0.99 (0.98, 1.00)
February	0.96	0.97 (0.96, 0.99)
March	1.20	0.97 (0.95, 0.98)
April	1.25	0.93 (0.91, 0.95)
May	0.96	0.96 (0.94, 0.98)
June	1.34	0.96 (0.95, 0.98)
July	1.02	0.92 (0.90, 0.95)
August	0.88	0.95 (0.93, 0.97)
September	1.20	0.99 (0.98, 1.00)
October	1.04	0.98 (0.97, 0.99)
November	1.02	0.97 (0.95, 0.99)
December	0.95	0.96 (0.94, 0.98)

Abbreviations: SAAR: Standardized Antimicrobial Administration Ratio (risk-adjusted total use)

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Chapter 6: Synthesis of Research

6.1 Overview and restatement of hypotheses

The overall objective of this dissertation research was to validate and refine the Standardized Antimicrobial Administration Ratio (SAAR), a metric developed by the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) to assist hospitals with their antimicrobial stewardship efforts. The SAAR metric provides a mechanism for facilities to track antibiotic utilization and benchmark performance against peer institutions;[1] however, direct comparison of antibiotic use between hospitals is complicated by differences in underlying patient and facility characteristics. This dissertation research focused on advancing the risk-adjustment methodology necessary for valid inter-hospital comparisons of antibiotic use, as well as testing the validity of using risk-adjusted total antibiotic use as a proxy for *appropriate* antibiotic use as a basis for the SAAR metric.

In Aim 1 (Chapter 3), I performed an external validation study using data from a nationwide network of hospitals (the Vizient Clinical Database and Resource Manager, CDB/RM™) to validate the 2014 CDC SAAR models as a measure for benchmarking inpatient antimicrobial use across facilities. I hypothesized that significant predictors of days of therapy (DOT) identified by the CDC would remain statistically significant in an external dataset.

In my second Aim (Chapter 4), I used the same CDB/RM™ dataset as in Aim 1 to develop antibiotic use prediction models to improve upon the risk-adjustment provided by the current SAAR metrics. I hypothesized that the addition

of new patient- and facility-level predictors would improve the performance of the CDC SAAR model for antibiotic agents predominantly used for resistant Gram-positive infections. I focused on this antibiotic category because these agents are frequently used in hospitalized patients, and vancomycin is one of the most common targets for stewardship interventions.

Finally, in Aim 3 (Chapter 5), I evaluated the validity of antibiotic benchmarking based on risk-adjusted total antibiotic use as a proxy for *appropriate* antibiotic use. The SAAR metrics do not take into consideration the indication for antibiotic use and as such, the validity of SAAR is unknown. I hypothesized that in a single healthcare facility over time, there is no association between benchmarking rankings based on a risk-adjusted total antibiotic use metric and rankings based on a measure of appropriate antibiotic use.

6.2 Summary of findings in context of study hypotheses

In Aim 1, all predictors identified by the CDC as statistically significant remained significant in all validation models except for three predictors: medical location type in the SAAR model for agents used for hospital-onset/multidrug-resistant infections, the interaction between intensive care unit (ICU) and medical/surgical location type in the anti-methicillin-resistant *Staphylococcus aureus* agent SAAR model, and ICU status in the surgical site infection prophylaxis SAAR model. In addition, while not statistically significant, two of the coefficients changed direction. These findings demonstrate that risk-adjustment with facility-

level predictors resulted in moderate performance of the SAAR models when tested in the validation dataset.

In Aim 2, I incorporated patient-level predictors of antibiotic use to improve upon the risk-adjustment of the SAAR model for agents used for resistant Gram-positive infections. Due to the high statistical power of my dataset, I used a combination of variable selection strategies, including machine learning approaches, to construct the final, parsimonious model. There were several aspects of my data that needed to be accounted for in my modeling approach: negative binomial distribution, overdispersion, zero-inflation, and clustering of patients within facilities. Constructing a patient-level model to predict DOT for Gram-positive agents proved to be a challenging undertaking, and as presented in Chapter 4, two models were developed.

I first developed a generalized estimating equation (GEE) negative binomial regression model and while the patient-level predictors and corresponding magnitudes of association were clinically sensible (e.g. diagnosis codes and length of stay in the ICU), the model consistently overpredicted DOT compared to observed DOT for each facility. Because the probability of excess zeros was not taken into account in the GEE model, I next constructed a zero-inflated negative binomial model. I was unable to compare performance of my two encounter-level models with that of the CDC SAAR model because of differences in modeling approach and thus direct comparison was not possible using a single fit statistic. However, I was able to evaluate the performance of my models by comparing observed-to-predicted DOT for each facility. The model that accounted for excess

zeros resulted in more accurate predictions of DOT compared to the GEE model that overpredicted DOT.

Results from Aim 3 suggest that in a single facility where appropriate use of antibacterial agents for resistant Gram-positive infections is high, benchmarking rankings using a risk-adjusted total antibiotic use metric was not associated with a measure of *appropriate* antibiotic use. In other words, total antibiotic use was not a valid proxy for appropriate antibiotic use. This is based on minimal correlation as assessed by Spearman Rank Correlation, as well as more than half of months changing rank by three or more positions.

In summary, this dissertation research challenges the existing paradigm of the use of a risk-adjusted antibiotic use metric to inform stewardship practice. While moderate performance of the SAAR models in the external validation study may be interpreted as a strength of the SAAR metric, risk-adjustment may be improved through use of patient-level characteristics. However, predicting antibiotic use at the patient-level is methodologically complex and additional work is needed to advance risk-adjustment methodology. Yet ultimately, the data suggest that risk-adjusted antibiotic use is not a valid proxy for appropriate use. As such the SAAR metric may provide misleading evidence for stewardship programs in their efforts to improve antibiotic use in the hospital setting.

6.3 Overall limitations and remaining questions

This dissertation research has important limitations. First, patient location in the hospital is a significant predictor of DOT in both the 2014 and 2017 SAAR

models.[1,2] In my Aim 1 external validation study, I did not have patient location data available at the time of antibiotic administration in the CDB/RM™ dataset. As such, I classified patient location based on accommodations data, which may be different from how facilities classify locations in NHSN. To minimize potential misclassification, I used diagnosis-related group (DRG) codes to map patients to locations where they likely received care. However, it is possible that some encounters were misclassified and I am unable to assess the magnitude and direction of any misclassification with the available data.

While facility-level predictors, such as patient location type, teaching status, and facility bed size are variables that are easy to collect via the NHSN, it remains unclear how meaningful these facility-level variables are in predicting antibiotic use. Notably, in my second Aim in which I used machine learning approaches to assist with variable selection, all facility-level predictors were excluded as candidate variables in the final model. Specifically, machine learning algorithms identified these facility-level variables as less important in predicting DOT than patient-level variables, such as diagnosis codes, sex, age, and days in the ICU. In the absence of patient-level data, NHSN uses facility-level variables as proxies for predicting antibiotic use. However, proxy variables are not causal variables, and as such may lack stability over time and place. Thus the validity of using proxy variables to risk-adjust DOT warrants further research.

A question arising from my second Aim is how best to use patient-level data to predict a complex outcome such as antibiotic DOT. While I found that a zero-inflated negative binomial model more accurately predicted DOT than a GEE

negative binomial model, this model has a complex interpretation. In addition, I was unable to account for clustering of patients within facilities in the model that accounted for excess zeros. This is a limitation of the zero-inflated model and identifying a modeling approach that accounts for the negative binomial distribution, overdispersion, clustering, and excess zeros present in the data remains to be determined. Finally, a limitation of the CDB/RM™ is that no culture data are available in the dataset; thus I was unable to include important known predictors of antibiotic use, such as organism and susceptibilities, to further optimize the prediction models.

In my third Aim I tested my hypothesis in a single antibiotic grouping (agents for resistant Gram-positive infections) in a single facility (Oregon Health & Science University, OHSU). As such, my results may not be generalizable to other antibacterial groupings. Next steps are to test the external validity of this finding in facilities beyond OHSU, as well as for other antibiotic categories. It is necessary to highlight the importance of the denominator in devising a measure to quantify appropriate antibiotic use. In the measure I used for appropriate antibiotic use, the denominator was comprised of total DOT, and the numerator was appropriate DOT. As constructed this way, the measure does not include encounters in which antibiotics were appropriately *not* used. Modifying the denominator to include total patient days, instead of total DOT, for example, may affect benchmarking rankings. The impact of using different denominators on benchmarking antibiotic use remains unknown.

6.4 Significance and contributions of this research

With the increasing public health burden of antibiotic resistance and the likelihood of government mandated antibiotic stewardship activities in the near future, it is imperative that measures of antibiotic utilization are scientifically valid. My dissertation work is the only research I am aware of that addresses the critical gap between antibiotic use measures, such as the SAAR, and antibiotic appropriateness. In addition, my research is the first to validate the 2014 SAAR models in an external validation study. Finally, this work adds to the emerging literature that risk-adjustment with patient-level predictors may result in more meaningful inter-hospital comparisons of antibiotic use.

As mentioned previously, the SAAR does not indicate if antibiotic use is appropriate or inappropriate, only if it is higher or lower than what is predicted. The most desired measure of antimicrobial use to assess the effectiveness of a stewardship program is a measure of *appropriate* use. To accurately evaluate antibiotic appropriateness, evaluation at the patient-level is necessary and as such, labor intensive. My dissertation research provides a first attempt at assessing the correlation between total antibiotic use and appropriate use as a method of benchmarking hospital performance. In our sample, the two measures had minimal correlation. While further work is needed to test the generalizability of these results, the methodology of assessing appropriateness using electronic health record (EHR) data was advanced in this aim of my research. Using EHR data combined with clinical criteria, I was able to reduce the burden of chart review

by nearly half, making assessments of antibiotic appropriateness a feasible undertaking.

As federal oversight of antibiotic stewardship increases, risk-adjusted benchmarking is expected to increase as well,[3] which has implications on both policy and public heath practice. SAAR is the first metric endorsed by the National Quality Forum as a quality performance measure for benchmarking antibiotic use,[2] and the Centers for Medicare and Medicaid Services (CMS) has proposed a rule tying SAAR to reimbursement policy.[4] This dissertation research highlights the complexities in predicting antibiotic use and contributes to the emerging evidence that case mix may not be adequately adjusted for by facility-level factors, and that patient-level characteristics such as diagnosis codes and comorbidities should be considered in risk adjustment.[5] Including patient-level factors in risk-adjustment is not a new endeavor and has been explored for healthcare-associated infections.[6-8] Extending this to risk-adjusted benchmarking of antibiotic use is a logical next step. However, further research is needed to optimize risk-adjustment methodology before an antibiotic use metric is accepted into practice or used for reimbursement purposes.

While the research community works to advance the science of risk-adjustment, the SAAR metric may be appropriate for evaluating antibiotic use within a single facility and/or patient location over time. Since the introduction of the SAAR metric into stewardship practice, recent studies have documented the utility of the measure in assessing the impact of stewardship interventions, such as prospective audit and feedback[9] and increased infectious disease physician

involvement in stewardship activities.[10] However, the best metric for fair comparison of performance *across* hospitals is yet to be determined.

6.5 Future directions

While significant effort went into the development of SAAR and it represents an important step forward in combating drug-resistant infections, this dissertation work further advances the field and highlights areas where additional research is needed. My Aim 1 research focused on validating the 2014 SAAR models, which are the first iteration of models. However, shortly after completing my validation study of the 2014 models, SAAR was re-baselined and the 2017 SAAR models were released. Future work should evaluate the external validity of the 2017 SAAR models as additional facility-level predictors were used in risk-adjustment of the newer set of models.

Prediction with patient-level data allows for use of causal variables in risk-adjustment, which may increase the validity and reproducibility of SAAR. However, facility-level data are easier to model because of the distribution of data and ease of variable collection. As such, advancements in risk-adjustment methodology are needed so that patient-level data can be incorporated into the prediction of DOT. Yet appropriate use is truly the ultimate target, and SAAR may not correlate well in high or low performing hospitals. Top performers may have high predicted antibiotic use, and there is a need to determine the best method for modeling performance at the tails-- meaning facilities with both very high and very low antibiotic use. Future research should focus on developing a valid metric that

provides actionable evidence for stewardship programs in their efforts to improve antibiotic use in the hospital and limit the spread of multi-drug resistant organisms.

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APPENDICES

Appendix A: Supplemental material for Chapter 3

Table A1. CDC SAAR model parameter estimates, by antibiotic use category[1]

Parameter	Estimate	Standard Error	Wald 95% Confidence Limits	
Model A: Broad-spectrum agents predominantly used for hospital-onset/multidrug-resistant infections				
Intercept	−2.669	0.081	−2.827	−2.511
ICU location[a]	0.971	0.052	0.868	1.074
Location type				
Medical unit	0.522	0.088	0.349	0.695
Medical/surgical unit	0.444	0.090	0.266	0.621
Surgical unit	0.406	0.098	0.213	0.598
Pediatric unit	Ref	...	...	...
Model B: Broad-spectrum agents predominantly used for community-acquired infections				
Intercept	−1.759	0.051	−1.859	−1.659
Teaching status	−0.376	0.055	−0.483	−0.268
ICU location[a]	0.122	0.049	0.026	0.219
Pediatric location	−0.202	0.079	−0.356	−0.047
Model C: Anti-MRSA agents				
Intercept	−3.506	0.097	−3.697	−3.316
ICU location[a]	1.432	0.208	1.023	1.840
Location type				
Medical unit	1.052	0.107	0.842	1.262
Medical/surgical unit	0.892	0.110	0.676	1.108
Surgical unit	1.095	0.123	0.853	1.337
Pediatric unit	Ref	...	...	...
Interaction of ICU and location type				
Medical unit	−0.521	0.227	−0.965	−0.077
Medical/surgical unit	−0.542	0.230	−0.993	−0.092
Surgical unit	−0.839	0.242	−1.313	−0.364
Pediatric unit	Ref	...	...	...
Model D: Agents predominantly used for surgical site infection prophylaxis				
Intercept	−3.288	0.055	−3.397	−3.180
ICU location[a]	0.343	0.099	0.148	0.537
Surgical location	0.967	0.115	0.741	1.193
Model E: All antibiotic agents				
Intercept	−0.786	0.053	−0.890	−0.683
ICU location[a]	0.501	0.034	0.433	0.568
Location type				
Medical unit	0.166	0.058	0.053	0.279
Medical/surgical unit	0.178	0.059	0.063	0.294
Surgical unit	0.140	0.064	0.014	0.266
Pediatric unit	Ref	...	...	...

Abbreviations: ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a]ICU location is an indicator variable (1/0) for a unit that is designated as a critical care location.

Appendix B: Supplemental material for Chapter 4

Table B1. Diagnosis-related group (DRG) codes, categorized by risk of receiving a Gram-positive antibiotic agent

DRG Code	DRG Name
Solid Organ Transplants	
1	HEART TRANSPLANT OR IMPLANT OF HEART ASSIST SYSTEM W MCC
2	HEART TRANSPLANT OR IMPLANT OF HEART ASSIST SYSTEM W/O MCC
5	LIVER TRANSPLANT W MCC OR INTESTINAL TRANSPLANT
6	LIVER TRANSPLANT WITHOUT MCC
7	LUNG TRANSPLANT
8	SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANT
10	PANCREAS TRANSPLANT
16	AUTOLOGOUS BONE MARROW TRANSPLANT WITH CC/MCC
17	AUTOLOGOUS BONE MARROW TRANSPLANT WITHOUT CC/MCC
652	KIDNEY TRANSPLANT
Bone Marrow Transplants	
14	ALLOGENEIC BONE MARROW TRANSPLANT
Orthopedic Operative	
466	REVISION OF HIP OR KNEE REPLACEMENT W MCC
467	REVISION OF HIP OR KNEE REPLACEMENT W CC
468	REVISION OF HIP OR KNEE REPLACEMENT W/O CC/MCC
469	MAJOR HIP AND KNEE JOINT REPLACEMENT OR REATTACHMENT OF LOWER EXTREMITY W MCC OR
470	MAJOR HIP AND KNEE JOINT REPLACEMENT OR REATTACHMENT OF LOWER EXTREMITY W/O MCC
480	HIP & FEMUR PROCEDURES EXCEPT MAJOR JOINT W MCC
481	HIP & FEMUR PROCEDURES EXCEPT MAJOR JOINT W CC
483	MAJOR JOINT/LIMB REATTACHMENT PROCEDURE OF UPPER EXTREMITIES
484	MAJOR JOINT & LIMB REATTACHMENT PROC OF UPPER EXTREMITY W/O CC/MCC
488	KNEE PROCEDURES W/O PDX OF INFECTION W CC/MCC
489	KNEE PROCEDURES W/O PDX OF INFECTION W/O CC/MCC
491	BACK & NECK PROC EXC SPINAL FUSION W/O CC/MCC
492	LOWER EXTREM & HUMER PROC EXCEPT HIP,FOOT,FEMUR W MCC
493	LOWER EXTREM & HUMER PROC EXCEPT HIP,FOOT,FEMUR W CC
506	MAJOR THUMB OR JOINT PROCEDURES
507	MAJOR SHOULDER OR ELBOW JOINT PROCEDURES W CC/MCC
508	MAJOR SHOULDER OR ELBOW JOINT PROCEDURES W/O CC/MCC
510	SHOULDER,ELBOW OR FOREARM PROC,EXC MAJOR JOINT PROC W MCC
511	SHOULDER,ELBOW OR FOREARM PROC,EXC MAJOR JOINT PROC W CC
518	BACK & NECK PROC EXC SPINAL FUSION W MCC OR DISC DEVICE/NEUROSTIM
520	BACK & NECK PROC EXC SPINAL FUSION W/O CC/MCC
Abdominal Operative	
326	STOMACH, ESOPHAGEAL & DUODENAL PROC W MCC
329	MAJOR SMALL & LARGE BOWEL PROCEDURES W MCC
332	RECTAL RESECTION W MCC
333	RECTAL RESECTION W CC
334	RECTAL RESECTION W/O CC/MCC
338	APPENDECTOMY W COMPLICATED PRINCIPAL DIAG W MCC
339	APPENDECTOMY W COMPLICATED PRINCIPAL DIAG W CC

340	APPENDECTOMY W COMPLICATED PRINCIPAL DIAG W/O CC/MCC
341	APPENDECTOMY W/O COMPLICATED PRINCIPAL DIAG W MCC
342	APPENDECTOMY W/O COMPLICATED PRINCIPAL DIAG W CC
343	APPENDECTOMY W/O COMPLICATED PRINCIPAL DIAG W/O CC/MCC
350	INGUINAL & FEMORAL HERNIA PROCEDURES W MCC
351	INGUINAL & FEMORAL HERNIA PROCEDURES W CC
352	INGUINAL & FEMORAL HERNIA PROCEDURES W/O CC/MCC
353	HERNIA PROCEDURES EXCEPT INGUINAL & FEMORAL W MCC
354	HERNIA PROCEDURES EXCEPT INGUINAL & FEMORAL W CC
355	HERNIA PROCEDURES EXCEPT INGUINAL & FEMORAL W/O CC/MCC
356	OTHER DIGESTIVE SYSTEM O.R. PROCEDURES W MCC
357	OTHER DIGESTIVE SYSTEM O.R. PROCEDURES W CC
358	OTHER DIGESTIVE SYSTEM O.R. PROCEDURES W/O CC/MCC
411	CHOLECYSTECTOMY W C.D.E. W MCC
412	CHOLECYSTECTOMY W C.D.E. W CC
413	CHOLECYSTECTOMY W C.D.E. W/O CC/MCC
414	CHOLECYSTECTOMY EXCEPT BY LAPAROSCOPE W/O C.D.E. W MCC
415	CHOLECYSTECTOMY EXCEPT BY LAPAROSCOPE W/O C.D.E. W CC
416	CHOLECYSTECTOMY EXCEPT BY LAPAROSCOPE W/O C.D.E. W/O CC/MCC
417	LAPAROSCOPIC CHOLECYSTECTOMY W/O C.D.E. W MCC
418	LAPAROSCOPIC CHOLECYSTECTOMY W/O C.D.E. W CC
419	LAPAROSCOPIC CHOLECYSTECTOMY W/O C.D.E. W/O CC/MCC
423	OTHER HEPATOBILIARY OR PANCREAS O.R. PROCEDURES W MCC
424	OTHER HEPATOBILIARY OR PANCREAS O.R. PROCEDURES W CC
425	OTHER HEPATOBILIARY OR PANCREAS O.R. PROCEDURES W/O CC/MCC
462	BILATERAL OR MULTIPLE MAJOR JOINT PROCS OF LOWER EXTREMITY W/O MCC
619	O.R. PROCEDURES FOR OBESITY W MCC
620	O.R. PROCEDURES FOR OBESITY W CC
621	O.R. PROCEDURES FOR OBESITY W/O CC/MCC
799	SPLENECTOMY W MCC
800	SPLENECTOMY W CC
801	SPLENECTOMY W/O CC/MCC
802	OTHER O.R. PROC OF THE BLOOD & BLOOD FORMING ORGANS W MCC
803	OTHER O.R. PROC OF THE BLOOD & BLOOD FORMING ORGANS W CC
804	OTHER O.R. PROC OF THE BLOOD & BLOOD FORMING ORGANS W/O CC/MCC
Obstetric Operative	
734	PELVIC EVISCERATION, RAD HYSTERECTOMY & RAD VULVECTOMY W CC/MCC
735	PELVIC EVISCERATION, RAD HYSTERECTOMY & RAD VULVECTOMY W/O CC/MCC
742	UTERINE & ADNEXA PROC FOR NON-MALIGNANCY W CC/MCC
743	UTERINE & ADNEXA PROC FOR NON-MALIGNANCY W/O CC/MCC
744	D&C, CONIZATION, LAPAROSCOPY & TUBAL INTERRUPTION W CC/MCC
745	D&C, CONIZATION, LAPAROSCOPY & TUBAL INTERRUPTION W/O CC/MCC
748	FEMALE REPRODUCTIVE SYSTEM RECONSTRUCTIVE PROCEDURES
749	OTHER FEMALE REPRODUCTIVE SYSTEM O.R. PROCEDURES W CC/MCC
750	OTHER FEMALE REPRODUCTIVE SYSTEM O.R. PROCEDURES W/O CC/MCC
765	CESAREAN SECTION W CC/MCC
766	CESAREAN SECTION W/O CC/MCC
767	VAGINAL DELIVERY W STERILIZATION &/OR D&C
768	VAGINAL DELIVERY W O.R. PROC EXCEPT STERIL &/OR D&C
769	POSTPARTUM & POST ABORTION DIAGNOSES W O.R. PROCEDURE
770	ABORTION W D&C, ASPIRATION CURETTAGE OR HYSTEROTOMY

776	POSTPARTUM & POST ABORTION DIAGNOSES W/O O.R. PROCEDURE
Neurology Operative	
25	CRANIOTOMY & ENDOVASCULAR INTRACRANIAL PROCEDURES W MCC
26	CRANIOTOMY & ENDOVASCULAR INTRACRANIAL PROCEDURES W CC
27	CRANIOTOMY & ENDOVASCULAR INTRACRANIAL PROCEDURES W/O CC/MCC
29	SPINAL PROCEDURES W CC OR SPINAL NEUROSTIMULATORS
30	SPINAL PROCEDURES W/O CC/MCC
37	EXTRACRANIAL PROCEDURES W MCC
40	PERIPH/CRANIAL NERVE & OTHER NERV SYST PROC W MCC
42	PERIPH/CRANIAL NERVE & OTHER NERV SYST PROC W/O CC/MCC
453	COMBINED ANTERIOR/POSTERIOR SPINAL FUSION W MCC
454	COMBINED ANTERIOR/POSTERIOR SPINAL FUSION W CC
455	COMBINED ANTERIOR/POSTERIOR SPINAL FUSION W/O CC/MCC
456	SPINAL FUS EXC CERV W SPINAL CURV/MALIG/INFEC OR EXT FUS W MCC
457	SPINAL FUS EXC CERV W SPINAL CURV/MALIG/INFEC OR EXT FUS W CC
458	SPINAL FUS EXC CERV W SPINAL CURV/MALIG/INFEC OR EXT FUS W/O CC/MCC
459	SPINAL FUSION EXCEPT CERVICAL W MCC
460	SPINAL FUSION EXCEPT CERVICAL W/O MCC
471	CERVICAL SPINAL FUSION W MCC
472	CERVICAL SPINAL FUSION W CC
473	CERVICAL SPINAL FUSION W/O CC/MCC
490	BACK & NECK PROC EXC SPINAL FUSION W CC/MCC OR DISC DEVICE/NEUROSTIM
519	BACK & NECK PROC EXC SPINAL FUSION W CC
Cardiothoracic Operative	
163	MAJOR CHEST PROCEDURES W MCC
164	MAJOR CHEST PROCEDURES W CC
165	MAJOR CHEST PROCEDURES W/O CC/MCC
220	CARDIAC VALVE & OTH MAJ CARDIOTHORACIC PROC W/O CARD CATH W CC
221	CARDIAC VALVE & OTH MAJ CARDIOTHORACIC PROC W/O CARD CATH W/O CC/MCC
231	CORONARY BYPASS W PTCA W MCC
232	CORONARY BYPASS W PTCA W/O MCC
233	CORONARY BYPASS W CARDIAC CATH W MCC
234	CORONARY BYPASS W CARDIAC CATH W/O MCC
235	CORONARY BYPASS W/O CARDIAC CATH W MCC
236	CORONARY BYPASS W/O CARDIAC CATH W/O MCC
237	MAJOR CARDIOVASC PROCEDURES W MCC
238	MAJOR CARDIOVASC PROCEDURES W/O MCC
266	ENDOVASCULAR CARDIAC VALVE REPLACEMENT W MCC
267	ENDOVASCULAR CARDIAC VALVE REPLACEMENT W/O MCC
270	OTHER MAJOR CARDIOVASCULAR PROCEDURES W MCC
Other Surgical	
129	MAJOR HEAD & NECK PROCEDURES W CC/MCC OR MAJOR DEVICE
130	MAJOR HEAD & NECK PROCEDURES W/O CC/MCC
133	OTHER EAR, NOSE, MOUTH & THROAT O.R. PROCEDURES W CC/MCC
134	OTHER EAR, NOSE, MOUTH & THROAT O.R. PROCEDURES W/O CC/MCC
166	OTHER RESP SYSTEM O.R. PROCEDURES W MCC
167	OTHER RESP SYSTEM O.R. PROCEDURES W CC
168	OTHER RESP SYSTEM O.R. PROCEDURES W/O CC/MCC
239	AMPUTATION FOR CIRC SYS DISORDERS EXC UPPER LIMB & TOE W MCC
240	AMPUTATION FOR CIRC SYS DISORDERS EXC UPPER LIMB & TOE W CC

241	AMPUTATION FOR CIRC SYS DISORDERS EXC UPPER LIMB & TOE W/O CC/MCC
255	UPPER LIMB & TOE AMPUTATION FOR CIRC SYSTEM DISORDERS W MCC
256	UPPER LIMB & TOE AMPUTATION FOR CIRC SYSTEM DISORDERS W CC
257	UPPER LIMB & TOE AMPUTATION FOR CIRC SYSTEM DISORDERS W/O CC/MCC
264	OTHER CIRCULATORY SYSTEM O.R. PROCEDURES
474	AMPUTATION FOR MUSCULOSKELETAL SYS & CONN TISSUE DIS W MCC
475	AMPUTATION FOR MUSCULOSKELETAL SYS & CONN TISSUE DIS W CC
476	AMPUTATION FOR MUSCULOSKELETAL SYS & CONN TISSUE DIS W/O CC/MCC
500	SOFT TISSUE PROCEDURES W MCC
501	SOFT TISSUE PROCEDURES W CC
513	HAND OR WRIST PROC, EXCEPT MAJOR THUMB OR JOINT PROC W CC/MCC
514	HAND OR WRIST PROC, EXCEPT MAJOR THUMB OR JOINT PROC W/O CC/MCC
515	OTHER MUSCULOSKELET SYS & CONN TISS O.R. PROC W MCC
516	OTHER MUSCULOSKELET SYS & CONN TISS O.R. PROC W CC
517	OTHER MUSCULOSKELET SYS & CONN TISS O.R. PROC W/O CC/MCC
582	MASTECTOMY FOR MALIGNANCY W CC/MCC
583	MASTECTOMY FOR MALIGNANCY W/O CC/MCC
616	AMPUTAT OF LOWER LIMB FOR ENDOCRINE,NUTRIT,& METABOL DIS W MCC
617	AMPUTAT OF LOWER LIMB FOR ENDOCRINE,NUTRIT,& METABOL DIS W CC
618	AMPUTAT OF LOWER LIMB FOR ENDOCRINE,NUTRIT,& METABOL DIS W/O CC/MCC
628	OTHER ENDOCRINE, NUTRIT & METAB O.R. PROC W MCC
629	OTHER ENDOCRINE, NUTRIT & METAB O.R. PROC W CC
630	OTHER ENDOCRINE, NUTRIT & METAB O.R. PROC W/O CC/MCC
660	KIDNEY & URETER PROCEDURES FOR NON-NEOPLASM W CC
661	KIDNEY & URETER PROCEDURES FOR NON-NEOPLASM W/O CC/MCC
665	PROSTATECTOMY W MCC
666	PROSTATECTOMY W CC
667	PROSTATECTOMY W/O CC/MCC
669	TRANSURETHRAL PROCEDURES W CC
670	TRANSURETHRAL PROCEDURES W/O CC/MCC
671	URETHRAL PROCEDURES W CC/MCC
713	TRANSURETHRAL PROSTATECTOMY W CC/MCC
714	TRANSURETHRAL PROSTATECTOMY W/O CC/MCC
715	OTHER MALE REPRODUCTIVE SYSTEM O.R. PROC FOR MALIGNANCY W CC/MCC
716	OTHER MALE REPRODUCTIVE SYSTEM O.R. PROC FOR MALIGNANCY W/O CC/MCC
717	OTHER MALE REPRODUCTIVE SYSTEM O.R. PROC EXC MALIGNANCY W CC/MCC
718	OTHER MALE REPRODUCTIVE SYSTEM O.R. PROC EXC MALIGNANCY W/O CC/MCC
876	O.R. PROCEDURE W PRINCIPAL DIAGNOSES OF MENTAL ILLNESS
907	OTHER O.R. PROCEDURES FOR INJURIES W MCC
908	OTHER O.R. PROCEDURES FOR INJURIES W CC
909	OTHER O.R. PROCEDURES FOR INJURIES W/O CC/MCC
939	O.R. PROC W DIAGNOSES OF OTHER CONTACT W HEALTH SERVICES W MCC
940	O.R. PROC W DIAGNOSES OF OTHER CONTACT W HEALTH SERVICES W CC

941	O.R. PROC W DIAGNOSES OF OTHER CONTACT W HEALTH SERVICES W/O CC/MCC
969	HIV W EXTENSIVE O.R. PROCEDURE W MCC
970	HIV W EXTENSIVE O.R. PROCEDURE W/O MCC
981	EXTENSIVE O.R. PROCEDURE UNRELATED TO PRINCIPAL DIAGNOSIS W MCC
982	EXTENSIVE O.R. PROCEDURE UNRELATED TO PRINCIPAL DIAGNOSIS W CC
983	EXTENSIVE O.R. PROCEDURE UNRELATED TO PRINCIPAL DIAGNOSIS W/O CC/MCC
984	PROSTATIC O.R. PROCEDURE UNRELATED TO PRINCIPAL DIAGNOSIS W MCC
985	PROSTATIC O.R. PROCEDURE UNRELATED TO PRINCIPAL DIAGNOSIS W CC
986	PROSTATIC O.R. PROCEDURE UNRELATED TO PRINCIPAL DIAGNOSIS W/O CC/MCC
987	NON-EXTENSIVE O.R. PROC UNRELATED TO PRINCIPAL DIAGNOSIS W MCC
988	NON-EXTENSIVE O.R. PROC UNRELATED TO PRINCIPAL DIAGNOSIS WITH CC
989	NON-EXTENSIVE O.R. PROC UNRELATED TO PRINCIPAL DIAGNOSIS W/O CC/MCC
Dialysis / Renal Failure	
682	RENAL FAILURE W MCC
683	RENAL FAILURE W CC
684	RENAL FAILURE W/O CC/MCC
685	ADMIT FOR RENAL DIALYSIS
Trauma	
82	TRAUMATIC STUPOR & COMA, COMA >1 HR W MCC
83	TRAUMATIC STUPOR & COMA, COMA >1 HR W CC
84	TRAUMATIC STUPOR & COMA, COMA >1 HR W/O CC/MCC
85	TRAUMATIC STUPOR & COMA, COMA <1 HR W MCC
86	TRAUMATIC STUPOR & COMA, COMA <1 HR W CC
87	TRAUMATIC STUPOR & COMA, COMA <1 HR W/O CC/MCC
183	MAJOR CHEST TRAUMA W MCC
184	MAJOR CHEST TRAUMA W CC
185	MAJOR CHEST TRAUMA W/O CC/MCC
463	WND DEBRID & SKN GRFT EXC HAND, FOR MUSCULO-CONN TISS DIS W MCC
464	WND DEBRID & SKN GRFT EXC HAND, FOR MUSCULO-CONN TISS DIS W CC
465	WND DEBRID & SKN GRFT EXC HAND, FOR MUSCULO-CONN TISS DIS W/O CC/MCC
570	SKIN DEBRIDEMENT W MCC
571	SKIN DEBRIDEMENT W CC
572	SKIN DEBRIDEMENT W/O CC/MCC
604	TRAUMA TO THE SKIN, SUBCUT TISS & BREAST W MCC
605	TRAUMA TO THE SKIN, SUBCUT TISS & BREAST W/O MCC
622	SKIN GRAFTS & WOUND DEBRID FOR ENDOC, NUTRIT & METAB DIS W MCC
623	SKIN GRAFTS & WOUND DEBRID FOR ENDOC, NUTRIT & METAB DIS W CC
624	SKIN GRAFTS & WOUND DEBRID FOR ENDOC, NUTRIT & METAB DIS W/O CC/MCC
901	WOUND DEBRIDEMENTS FOR INJURIES W MCC
902	WOUND DEBRIDEMENTS FOR INJURIES W CC
903	WOUND DEBRIDEMENTS FOR INJURIES W/O CC/MCC
913	TRAUMATIC INJURY W MCC
914	TRAUMATIC INJURY W/O MCC
955	CRANIOTOMY FOR MULTIPLE SIGNIFICANT TRAUMA
956	LIMB REATTACHMENT, HIP & FEMUR PROC FOR MULTIPLE SIGNIFICANT TRAUMA

957	OTHER O.R. PROCEDURES FOR MULTIPLE SIGNIFICANT TRAUMA W MCC
958	OTHER O.R. PROCEDURES FOR MULTIPLE SIGNIFICANT TRAUMA W CC
959	OTHER O.R. PROCEDURES FOR MULTIPLE SIGNIFICANT TRAUMA W/O CC/MCC
963	OTHER MULTIPLE SIGNIFICANT TRAUMA W MCC
964	OTHER MULTIPLE SIGNIFICANT TRAUMA W CC
965	OTHER MULTIPLE SIGNIFICANT TRAUMA W/O CC/MCC
Burns	
927	EXTENSIVE BURNS OR FULL THICKNESS BURNS W MV >96 HRS W SKIN GRAFT
928	FULL THICKNESS BURN W SKIN GRAFT OR INHAL INJ W CC/MCC
929	FULL THICKNESS BURN W SKIN GRAFT OR INHAL INJ W/O CC/MCC
933	EXTENSIVE BURNS OR FULL THICKNESS BURNS W MV >96 HRS W/O SKIN GRAFT
934	FULL THICKNESS BURN W/O SKIN GRFT OR INHAL INJ
935	NON-EXTENSIVE BURNS
Infections not likely caused by *Staphylococcus aureus*	
152	OTITIS MEDIA & URI W MCC
153	OTITIS MEDIA & URI W/O MCC
202	BRONCHITIS & ASTHMA W CC/MCC
203	BRONCHITIS & ASTHMA W/O CC/MCC
371	MAJOR GASTROINTESTINAL DISORDERS & PERITONEAL INFECTIONS W MCC
372	MAJOR GASTROINTESTINAL DISORDERS & PERITONEAL INFECTIONS W CC
373	MAJOR GASTROINTESTINAL DISORDERS & PERITONEAL INFECTIONS W/O CC/MCC
485	KNEE PROCEDURES W PDX OF INFECTION W MCC
486	KNEE PROCEDURES W PDX OF INFECTION W CC
487	KNEE PROCEDURES W PDX OF INFECTION W/O CC/MCC
689	KIDNEY & URINARY TRACT INFECTIONS W MCC
690	KIDNEY & URINARY TRACT INFECTIONS W/O MCC
757	INFECTIONS, FEMALE REPRODUCTIVE SYSTEM W MCC
758	INFECTIONS, FEMALE REPRODUCTIVE SYSTEM W CC
759	INFECTIONS, FEMALE REPRODUCTIVE SYSTEM W/O CC/MCC
853	INFECTIOUS & PARASITIC DISEASES W O.R. PROCEDURE W MCC
854	INFECTIOUS & PARASITIC DISEASES W O.R. PROCEDURE W CC
855	INFECTIOUS & PARASITIC DISEASES W O.R. PROCEDURE W/O CC/MCC
856	POSTOPERATIVE OR POST-TRAUMATIC INFECTIONS W O.R. PROC W MCC
857	POSTOPERATIVE OR POST-TRAUMATIC INFECTIONS W O.R. PROC W CC
858	POSTOPERATIVE OR POST-TRAUMATIC INFECTIONS W O.R. PROC W/O CC/MCC
862	POSTOPERATIVE & POST-TRAUMATIC INFECTIONS W MCC
863	POSTOPERATIVE & POST-TRAUMATIC INFECTIONS W/O MCC
865	VIRAL ILLNESS W MCC
866	VIRAL ILLNESS W/O MCC
867	OTHER INFECTIOUS & PARASITIC DISEASES DIAGNOSES W MCC
868	OTHER INFECTIOUS & PARASITIC DISEASES DIAGNOSES W CC
869	OTHER INFECTIOUS & PARASITIC DISEASES DIAGNOSES W/O CC/MCC
Infections requiring empiric methicillin-resistant *Staphylococcus aureus* (MRSA) coverage	
75	VIRAL MENINGITIS W CC/MCC
76	VIRAL MENINGITIS W/O CC/MCC
94	BACTERIAL & TUBERCULOUS INFECTIONS OF NERVOUS SYSTEM W MCC
95	BACTERIAL & TUBERCULOUS INFECTIONS OF NERVOUS SYSTEM W CC

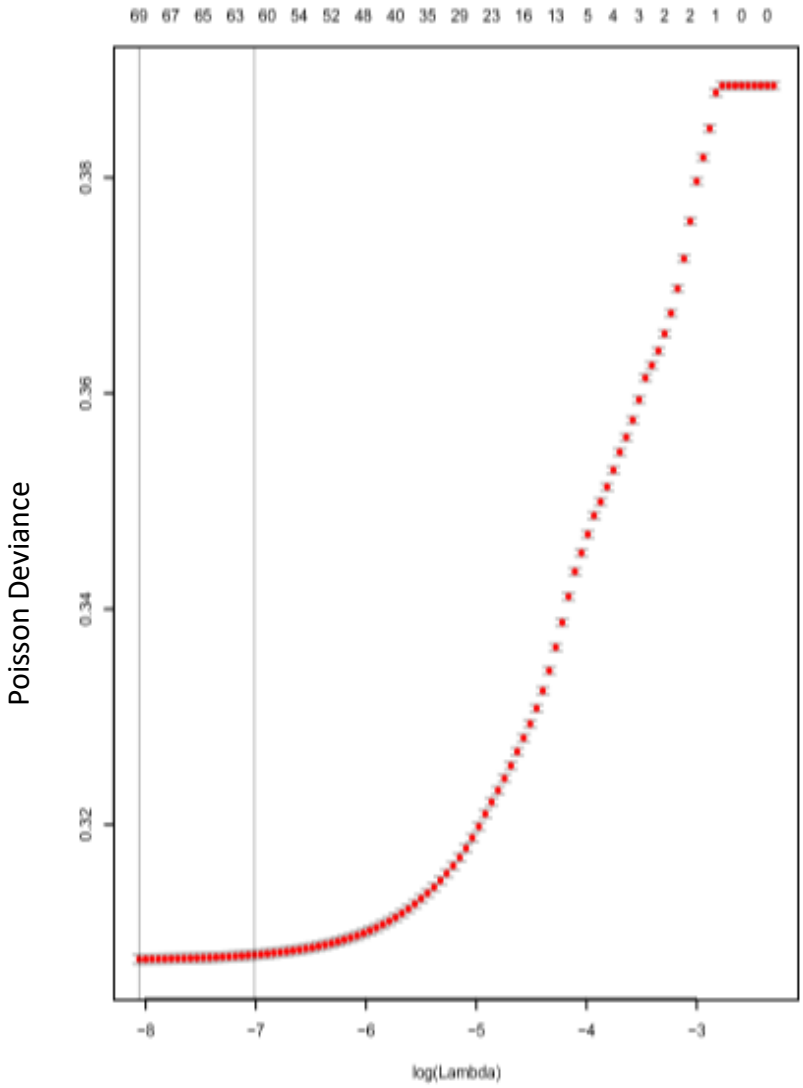
96	BACTERIAL & TUBERCULOUS INFECTIONS OF NERVOUS SYSTEM W/O CC/MCC
97	NON-BACTERIAL INFECT OF NERVOUS SYS EXC VIRAL MENINGITIS W MCC
98	NON-BACTERIAL INFECT OF NERVOUS SYS EXC VIRAL MENINGITIS W CC
99	NON-BACTERIAL INFECT OF NERVOUS SYS EXC VIRAL MENINGITIS W/O CC/MCC
121	ACUTE MAJOR EYE INFECTIONS W CC/MCC
122	ACUTE MAJOR EYE INFECTIONS W/O CC/MCC
177	RESPIRATORY INFECTIONS & INFLAMMATIONS W MCC
178	RESPIRATORY INFECTIONS & INFLAMMATIONS W CC
179	RESPIRATORY INFECTIONS & INFLAMMATIONS W/O CC/MCC
186	PLEURAL EFFUSION W MCC
187	PLEURAL EFFUSION W CC
188	PLEURAL EFFUSION W/O CC/MCC
193	SIMPLE PNEUMONIA & PLEURISY W MCC
194	SIMPLE PNEUMONIA & PLEURISY W CC
195	SIMPLE PNEUMONIA & PLEURISY W/O CC/MCC
864	FEVER
870	SEPTICEMIA OR SEVERE SEPSIS W MV >96 HOURS
871	SEPTICEMIA OR SEVERE SEPSIS W/O MV >96 HOURS W MCC
872	SEPTICEMIA OR SEVERE SEPSIS W/O MV >96 HOURS W/O MCC
Infections highly likely due to *Staphylococcus aureus*	
548	SEPTIC ARTHRITIS W MCC
549	SEPTIC ARTHRITIS W CC
550	SEPTIC ARTHRITIS W/O CC/MCC
573	SKIN GRAFT FOR SKIN ULCER OR CELLULITIS W MCC
574	SKIN GRAFT FOR SKIN ULCER OR CELLULITIS W CC
575	SKIN GRAFT FOR SKIN ULCER OR CELLULITIS W/O CC/MCC
576	SKIN GRAFT EXC FOR SKIN ULCER OR CELLULITIS W MCC
577	SKIN GRAFT EXC FOR SKIN ULCER OR CELLULITIS W CC
578	SKIN GRAFT EXC FOR SKIN ULCER OR CELLULITIS W/O CC/MCC
602	CELLULITIS W MCC
603	CELLULITIS W/O MCC
Infections likely to receive long-term methicillin-resistant *Staphylococcus aureus* (MRSA) coverage	
288	ACUTE & SUBACUTE ENDOCARDITIS W MCC
289	ACUTE & SUBACUTE ENDOCARDITIS W CC
290	ACUTE & SUBACUTE ENDOCARDITIS W/O CC/MCC
539	OSTEOMYELITIS W MCC
540	OSTEOMYELITIS W CC
541	OSTEOMYELITIS W/O CC/MCC
Invasive life support	
3	ECMO OR TRACH W MV >96 HRS OR PDX EXC FACE, MOUTH & NECK W MAJ O.R.
4	TRACH W MV >96 HRS OR PDX EXC FACE, MOUTH & NECK W/O MAJ O.R.
11	TRACHEOSTOMY FOR FACE,MOUTH & NECK DIAGNOSES W MCC
12	TRACHEOSTOMY FOR FACE,MOUTH & NECK DIAGNOSES W CC
13	TRACHEOSTOMY FOR FACE,MOUTH & NECK DIAGNOSES W/O CC/MCC
207	RESPIRATORY SYSTEM DIAGNOSIS W VENTILATOR SUPPORT >96 HOURS
208	RESPIRATORY SYSTEM DIAGNOSIS W VENTILATOR SUPPORT <=96 HOURS
Implantable device; shunt	
23	CRANIOTOMY W MAJOR DEVICE IMPLANT OR ACUTE CNS PDX W MCC OR CHEMOTHERAPY IMPLANT
24	CRANIO W MAJOR DEV IMPL/ACUTE COMPLEX CNS PDX W/O MCC

31	VENTRICULAR SHUNT PROCEDURES W MCC
32	VENTRICULAR SHUNT PROCEDURES W CC
33	VENTRICULAR SHUNT PROCEDURES W/O CC/MCC
215	OTHER HEART ASSIST SYSTEM IMPLANT
222	CARDIAC DEFIB IMPLANT W CARDIAC CATH W AMI/HF/SHOCK W MCC
223	CARDIAC DEFIB IMPLANT W CARDIAC CATH W AMI/HF/SHOCK W/O MCC
224	CARDIAC DEFIB IMPLANT W CARDIAC CATH W/O AMI/HF/SHOCK W MCC
225	CARDIAC DEFIB IMPLANT W CARDIAC CATH W/O AMI/HF/SHOCK W/O MCC
226	CARDIAC DEFIBRILLATOR IMPLANT W/O CARDIAC CATH W MCC
227	CARDIAC DEFIBRILLATOR IMPLANT W/O CARDIAC CATH W/O MCC
242	PERMANENT CARDIAC PACEMAKER IMPLANT W MCC
243	PERMANENT CARDIAC PACEMAKER IMPLANT W CC
244	PERMANENT CARDIAC PACEMAKER IMPLANT W/O CC/MCC
258	CARDIAC PACEMAKER DEVICE REPLACEMENT W MCC
259	CARDIAC PACEMAKER DEVICE REPLACEMENT W/O MCC
260	CARDIAC PACEMAKER REVISION EXCEPT DEVICE REPLACEMENT W MCC
261	CARDIAC PACEMAKER REVISION EXCEPT DEVICE REPLACEMENT W CC
262	CARDIAC PACEMAKER REVISION EXCEPT DEVICE REPLACEMENT W/O CC/MCC
405	PANCREAS, LIVER & SHUNT PROCEDURES W MCC
406	PANCREAS, LIVER & SHUNT PROCEDURES W CC
407	PANCREAS, LIVER & SHUNT PROCEDURES W/O CC/MCC
495	LOCAL EXCISION & REMOVAL INT FIX DEVICES EXC HIP & FEMUR W MCC
496	LOCAL EXCISION & REMOVAL INT FIX DEVICES EXC HIP & FEMUR W CC
497	LOCAL EXCISION & REMOVAL INT FIX DEVICES EXC HIP & FEMUR W/O CC/MCC
498	LOCAL EXCISION & REMOVAL INT FIX DEVICES OF HIP & FEMUR W CC/MCC
499	LOCAL EXCISION & REMOVAL INT FIX DEVICES OF HIP & FEMUR W/O CC/MCC
Solid tumors	
54	NERVOUS SYSTEM NEOPLASMS W MCC
55	NERVOUS SYSTEM NEOPLASMS W/O MCC
146	EAR, NOSE, MOUTH & THROAT MALIGNANCY W MCC
147	EAR, NOSE, MOUTH & THROAT MALIGNANCY W CC
148	EAR, NOSE, MOUTH & THROAT MALIGNANCY W/O CC/MCC
180	RESPIRATORY NEOPLASMS W MCC
181	RESPIRATORY NEOPLASMS W CC
182	RESPIRATORY NEOPLASMS W/O CC/MCC
374	DIGESTIVE MALIGNANCY W MCC
375	DIGESTIVE MALIGNANCY W CC
376	DIGESTIVE MALIGNANCY W/O CC/MCC
435	MALIGNANCY OF HEPATOBILIARY SYSTEM OR PANCREAS W MCC
436	MALIGNANCY OF HEPATOBILIARY SYSTEM OR PANCREAS W CC
437	MALIGNANCY OF HEPATOBILIARY SYSTEM OR PANCREAS W/O CC/MCC
543	PATHOLOGICAL FRACTURES & MUSCULOSKELET & CONN TISS MALIG W CC
597	MALIGNANT BREAST DISORDERS W MCC
598	MALIGNANT BREAST DISORDERS W CC
599	MALIGNANT BREAST DISORDERS W/O CC/MCC
656	KIDNEY & URETER PROCEDURES FOR NEOPLASM W MCC
657	KIDNEY & URETER PROCEDURES FOR NEOPLASM W CC
658	KIDNEY & URETER PROCEDURES FOR NEOPLASM W/O CC/MCC
686	KIDNEY & URINARY TRACT NEOPLASMS W MCC
687	KIDNEY & URINARY TRACT NEOPLASMS W CC
688	KIDNEY & URINARY TRACT NEOPLASMS W/O CC/MCC

722	MALIGNANCY, MALE REPRODUCTIVE SYSTEM W MCC
723	MALIGNANCY, MALE REPRODUCTIVE SYSTEM W CC
724	MALIGNANCY, MALE REPRODUCTIVE SYSTEM W/O CC/MCC
736	UTERINE & ADNEXA PROC FOR OVARIAN OR ADNEXAL MALIGNANCY W MCC
737	UTERINE & ADNEXA PROC FOR OVARIAN OR ADNEXAL MALIGNANCY W CC
738	UTERINE & ADNEXA PROC FOR OVARIAN OR ADNEXAL MALIGNANCY W/O CC/MCC
739	UTERINE,ADNEXA PROC FOR NON-OVARIAN/ADNEXAL MALIG W MCC
740	UTERINE,ADNEXA PROC FOR NON-OVARIAN/ADNEXAL MALIG W CC
741	UTERINE,ADNEXA PROC FOR NON-OVARIAN/ADNEXAL MALIG W/O CC/MCC
754	MALIGNANCY, FEMALE REPRODUCTIVE SYSTEM W MCC
755	MALIGNANCY, FEMALE REPRODUCTIVE SYSTEM W CC
756	MALIGNANCY, FEMALE REPRODUCTIVE SYSTEM W/O CC/MCC
Hematologic disorders	
820	LYMPHOMA & LEUKEMIA W MAJOR O.R. PROCEDURE W MCC
821	LYMPHOMA & LEUKEMIA W MAJOR O.R. PROCEDURE W CC
822	LYMPHOMA & LEUKEMIA W MAJOR O.R. PROCEDURE W/O CC/MCC
824	LYMPHOMA & NON-ACUTE LEUKEMIA W OTHER PROC W CC
825	LYMPHOMA & NON-ACUTE LEUKEMIA W OTHER PROC W/O CC/MCC
826	MYELOPROLIF DISORD OR POORLY DIFF NEOPL W MAJ O.R. PROC W MCC
827	MYELOPROLIF DISORD OR POORLY DIFF NEOPL W MAJ O.R. PROC W CC
828	MYELOPROLIF DISORD OR POORLY DIFF NEOPL W MAJ O.R. PROC W/O CC/MCC
829	MYELOPROLIFERATIVE DISORDERS OR POORLY DIFFERENTIATED NEOPLASMS W OTHER PROCEDURE
830	MYELOPROLIFERATIVE DISORDERS OR POORLY DIFFERENTIATED NEOPLASMS W OTHER PROCEDURE
834	ACUTE LEUKEMIA W/O MAJOR O.R. PROCEDURE W MCC
835	ACUTE LEUKEMIA W/O MAJOR O.R. PROCEDURE W CC
836	ACUTE LEUKEMIA W/O MAJOR O.R. PROCEDURE W/O CC/MCC
837	CHEMO W ACUTE LEUKEMIA AS SDX OR W HIGH DOSE CHEMO AGENT W MCC
838	CHEMO W ACUTE LEUKEMIA AS SDX W CC OR HIGH DOSE CHEMO AGENT
839	CHEMO W ACUTE LEUKEMIA AS SDX W/O CC/MCC
840	LYMPHOMA & NON-ACUTE LEUKEMIA W MCC
841	LYMPHOMA & NON-ACUTE LEUKEMIA W CC
842	LYMPHOMA & NON-ACUTE LEUKEMIA W/O CC/MCC
843	OTHER MYELOPROLIF DIS OR POORLY DIFF NEOPL DIAG W MCC
844	OTHER MYELOPROLIF DIS OR POORLY DIFF NEOPL DIAG W CC
846	CHEMOTHERAPY W/O ACUTE LEUKEMIA AS SECONDARY DIAGNOSIS W MCC
847	CHEMOTHERAPY W/O ACUTE LEUKEMIA AS SECONDARY DIAGNOSIS W CC
848	CHEMOTHERAPY W/O ACUTE LEUKEMIA AS SECONDARY DIAGNOSIS W/O CC/MCC

All DRG codes not listed in table are the in referent group, and categorized as ‘Medical, other’.

Figure B1. GLMNET LASSO pathway at each step



Appendix C: Supplemental material for Chapter 5

Table C1. Parameter estimates for 2017 CDC SAAR model for agents predominantly used for resistant Gram-positive infections[2]

Parameter	Estimate	Standard Error	Wald 95% Confidence Limits	
Intercept	-4.0018	0.200	-4.393	-3.611
Location type				
Medical ICU, Medical-Surgical ICU, Surgical ICU	0.8382	0.032	0.775	0.902
Med Ward, Med-Surg Ward, General Hematology-Oncology, Step-down	0.1443	0.029	0.088	0.201
Surgical Ward	REF	.	.	.
Facility type				
Critical access, General acute care, Oncology, Surgical, Veteran's Affairs	1.1291	0.195	0.748	1.510
Military	0.7007	0.202	0.305	1.097
Women's, Women's & Children's	REF	.	.	.
Number of hospital beds, facility-wide				
≥66	0.1619	0.036	0.091	0.233
<66	REF	.	.	.
Average length of stay, facility-wide (in days)				
≥3.3	0.1913	0.027	0.139	0.244
<3.3	REF	.	.	.

References

1. van Santen KL, Edwards JR, Webb AK, et al. The Standardized Antimicrobial Administration Ratio: A New Metric for Measuring and Comparing Antibiotic Use. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2018;67:179-185.

2. National Quality Forum. *National Healthcare Safety Network (NHSN) Antimicrobial Use Measure*. 2018: Washington DC.