BUGS, DRUGS AND DATA: ANTIBIOTIC RESISTANCE, PREVALENCE AND PREDICTION OF BUG-DRUG MISMATCH USING ELECTRONIC HEALTH RECORDS (EHR) DATA

A DISSERTATION IN
Biomedical and Health Informatics,
Computer Science
and
Molecular Biology and Biochemistry

Presented to the Faculty of the University
of Missouri-Kansas City in partial fulfillment
of the requirements of the degree

DOCTOR OF PHILOSOPHY

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2021

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ABSTRACT

Bug-Drug Mismatch (BDM) occurrences are an important and modifiable category of inappropriate antibiotic therapy (IAAT) that increases adverse outcomes for patients and drives overall antibiotic resistance (AR). Surveillance of baseline AR, emerging trends in resistance among priority bacterial pathogens and prevalence of BDM with respect to the age of the patients and the type of health care-setting are required due to differences in antimicrobial need and use in these populations. Additionally, very little is known about the risk factors associated with BDM occurrence.

We performed a retrospective study using de-identified, electronic health record (EHR) data in the Cerner Health Facts™ data warehouse. We assessed antibiotic susceptibility data between the years 2012 to 2017 and visualized the slope coefficient from linear regression to compare changes in resistance over time. We examined the prevalence of BDM for critically important antibiotics and clinically relevant pathogens between the year 2009 to 2017 in four groups of patients: adults; children; children treated in freestanding pediatric facilities and children treated in blended facilities (adults and children). We implemented multiple logistic regression as a reference model to identify risk factors for BDM occurrences and compared the predictive performance

measure with 4 machine learning models (logistic regression with lasso regularization, random forest, gradient boosted decision tree and deep neural network).

The trends in resistance rates to clinically relevant antibiotics were influenced by age and care setting. BDM prevalence for several critically important antibiotics differed between children and adults as well as within pediatric and blended facilities. Risk factors such as age of the patient, patient comorbidities and size of the facility were significantly associated with BDM occurrence. Additionally, the machine learning models developed in our study has a high predictive ability (C-statistic), higher sensitivity, specificity, positive predictive value and positive likelihood ratio to identify BDM occurrence than the reference model.

This study describes the utility of data visualization to interpret large scale EHR data on the trends of AR, prevalence and risk factors of BDM which are critical in tailoring antibiotic stewardship efforts to improving appropriate antibiotic prescribing and ultimately reduce AR.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Graduate Studies have examined a thesis titled "Tracking the threat of antibiotic resistance using electronic health record (EHR) data: Emerging trends in bacterial resistance, prevalence and prediction of bug-drug mismatch occurrence", presented by Shivani Sivasankar, candidate for the Doctor of Philosophy degree, and certify that in their opinion it is worthy of acceptance.

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LIST OF ABBREVIATIONS

AR	- Antibiotic Resistance
BDM	- Bug-Drug Mismatch
CDC	- Center for Disease Control and Prevention
WHO	- World Health Organization
ASP	- Antibiotic Stewardship Policy
HAI	- Hospital Acquired Infection
IAAT	- Inappropriate Antibiotic Therapy
ML	-Machine Learning
MCS	- Multiple Categorical Slope Plot
C-MCS	-Comparison Multiple Categorical Slope Plot
MRSA	-Methicillin Resistant Staphylococcus aureus
MSSA	-Methicillin Susceptible Staphylococcus aureus
VRE	-Vancomycin Resistant Enterococcus

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Dr. Mark Hoffman, my research advisor and mentor for his patience, motivation, enthusiasm, immense knowledge, unwavering support over the last four years and giving me the opportunity to pursue my research interest at Children's Mercy Research Institute. His guidance helped me throughout this research and writing the thesis. I could not have imagined having a better advisor and mentor for my Ph.D. study. I would like to extend my gratitude to Dr. An-Lin Cheng for her instructions, guidance, progress monitoring, and support. I would also like to express my gratitude to Dr. Jenifer Goldman, for the encouragement, guidance and supervision. Without her passionate participation and input, this research could not have been successfully conducted. Many thanks to Dr. Yugyung Lee for introducing me to machine learning and for her help in reviewing the machine learning models used in this research. I'm also thankful to Dr. Gerald Wyckoff, for the time he took to review my work and provide valuable feedback. I would also like to extend my gratitude to my colleagues, Cathy Jackson, Sierra Martin, Earl Glynn and Dr. Natalie Kane for their helpful comments and immense support towards my Ph.D. study and research. My last, but certainly not least, acknowledgement goes to my parents Sivasankar and Vijayalakshmi, my partner Deepak Sireeshan and all my friends for supporting me throughout these years. I wouldn't be where I am without the love, help, and encouragement from you all. Thank you.

CHAPTER 1

INTRODUCTION

1.1. Motivation

Antibiotics have been a critical public health tool since the discovery of penicillin in 1928, saving the lives of millions of people around the world (1). Today, however, the emergence of drug resistance in bacteria is reversing the advances of the past eighty years, with drug choices for the treatment of many bacterial infections becoming increasingly limited, expensive, and, in some cases, nonexistent (2). Antibiotic-resistant (AR) pathogens infect more than 2.8 million Americans, and more than 35,000 people die each year (3). In 2013, the Center for Disease Control and Prevention (CDC) implemented the Antibiotic Resistance Solution (ARS) initiative with the objective: (i) to detect and respond to emerging trends in resistance; (ii) to identify track and understand antibiotic use data; (iii) to direct hospital antibiotic stewardship programs (ASP) to improve patient outcomes (4). These strategies were proven to be effective as there were 28% fewer deaths from AR in hospitals since the ARS initiative (5). In this dissertation, we identified specific areas to improve the ARS framework which could further aid to stem the threat of AR.

Identifying emerging patterns of antibiotic resistance is necessary for providers to effectively tailor antibiotic therapy (6–8). Antibiotic resistance is a global public health threat that continues to escalate and impact all populations, however, until recently, trends in drug resistant infections in children have been relatively uncharacterized.

Isolates from children have different selective pressure due to their evolving immune system, increased risk of adverse events or overall antimicrobial exposure (9, 10). The type of facility (standalone pediatric or blended facilities caring for adults and children) could also be a factor for different resistance patterns in children, especially in Hospital Acquired Infections (HAI) (11). Substantial differences between pediatric and blended facilities exist, including patient characteristics, medical training programs, and clinical outcomes (12–14). Pediatric facilities have also been found to vary substantially in their use of antibiotics (15). However, there are no studies that have compared AR patterns for priority pathogens between children and adults nor between types of facility.

Bug-Drug Mismatch (BDM) occurrences are an important and modifiable category of inappropriate antibiotic therapy (IAAT) that increases adverse outcomes for patients and drives overall antibiotic resistance (16). Considering, antibiotic use varies significantly between children and adults (17, 18), very few studies have evaluated appropriate antibiotic use in US hospitals within pediatric populations, and these reflect only single centers or specific diagnoses or interventions (19–22). And there are no studies that provide estimates on the prevalence of BDM occurrence on pediatric population between pediatric and blended facilities.

Patients with a BDM occurrence have questionable therapeutic benefit and increasing adverse outcomes as the patient is prescribed incorrect antibiotic to which the pathogen is resistant (23). However, little information exists on the identification of independent risk factors for BDM occurrence which may be useful for the development of preventive measures like development of Clinical Decision Support (CDS) tools as part of ASP initiatives (24, 25). While most of the published IAAT prediction studies

have focused on logistic regression models, ML models have potential in solving complex and challenging clinical outcome problems (26–31). Although there are ML studies recently published on predicting antibiotic resistance (32–34), there are no studies that have evaluated the utility of predicting BDM occurrence.

1.2. Objectives

The objectives of the dissertation are to:

1. Compare the prevalence of AR and trends in resistance for the priority bacterial pathogens between children and adults as well as among children treated in primarily pediatric facilities and blended facilities.
2. Compare the prevalence of BDM occurrence at the antibiotic level and pathogen level between children and adults as well as among children treated in primarily pediatric facilities and blended facilities.
3. Identify the risk factors associated with BDM occurrence using logistic regression.
4. Develop machine learning models that predict the occurrence of BDM and compare their prediction performance with the reference logistic regression model.

1.3. Dissertation Content

Chapter 2 provides a brief background on the microbiology of bacteria, general approach to infection diseases, basis of antibiotic resistance, increasing trend in antibiotic resistance, complex determinants of inappropriate antibiotic use, consequences of antibiotic resistance and bug-drug mismatch, initiatives in Antibiotic Stewardship Programs and machine learning algorithms implemented in healthcare. Study methodology, data extraction, statistical analyses, results and discussion are presented in:

Chapter 3 for the evaluation of baseline AR prevalence and emerging trends in AR between adults and children as well pediatric and blended facilities; Chapter 4 for the prevalence of BDM at the antibiotic level and pathogen level between adults and children as well pediatric and blended facilities; Chapter 5 for identification of risk factor for BDM and comparing the prediction ability of logistic regression with machine learning techniques. Chapter 7 serves as the conclusion, where the major findings, strengths and limitations of the study are delineated and possible future directions for this research are explored.

CHAPTER 2

BACKGROUND

2.1. Microbiology of Bacteria

The development of bacterial resistance to antibiotics is one of the best documented cases of rapid evolution. This section covers a brief overview of the microbial world. Bacteria such as *Escherichia coli, Streptococcus pneumoniae and Staphylococcus aureus* are both normal commensal flora and occasionally, pathogens which are responsible for infection. Therefore, growth of one of these organisms from a culture is not necessarily synonymous with infection. Suspicion of infection is increased greatly if the bacteria grows from a sterile site such as the bloodstream, abscess or cerebrospinal fluid (CSF) rather than non-sterile sites such as skin and sputum (35, 36). Definitive identification and susceptibility testing may take anywhere from hours to weeks, depending on the organism and the testing method. For bacteria, the most important identification method is the Gram stain which selectively stains the cell walls of Gram-positive bacteria but not of Gram-negative bacteria due to the absence of an outer cell wall (37). Rapid identification of bacteria based on morphology, colony clustering and preliminary biochemical tests can help to direct therapy.

2.2. General Approach to Infectious Diseases

To protect the human body from the onslaught of bacterial pathogens, a large number of antimicrobial compounds have been developed that target points of vulnerability within these invaders. These agents can be grouped into three broad categories based on their mechanism of action: (1) those that target the bacterial cell envelope, (2) those that block the production of new proteins, (3) those that target DNA or DNA replication (35, 38). The susceptibility of a bacterial isolate to a given antibiotic is quantified by minimum inhibitory concentration (MIC). For every pathogen- antibiotic combination, there is a particular cut off MIC that defines susceptibility. Several assays such as the Kirby-Bauer method, E-tests and broth dilution methods, have been developed to measure whether any given bacterial isolate is susceptible or resistant to a particular antibiotic (39).

The use of antibiotics falls into one of three general categories: prophylaxis, empiric use and definitive therapy. Prophylaxis is the treatment given to prevent an infection that has not yet developed such as those given to patients on immunosuppressive therapy (40). Empiric therapy is given to patients who have a suspected infection, but the responsible organisms have not yet been identified. Definitive therapy is given to patients after the bacterial culture and antibiotic sensitivity results are known (41). The major selection pressure driving changes in the frequency of antibiotic resistance is the volume of drug use. On a daily basis, clinicians are forced to choose an antibiotic for a patient with symptoms and signs of a serious infection before identification of the bacteria and before susceptibility test results are available. Such treatment can be described as initial empiric therapy initiated on the basis of (1)

symptoms of the patient, formal review of previously isolated organisms and prior antibiotic use, (2) using unit-based antibiograms, and (3) using data from surveillance studies. When identification and susceptibility testing results are available to the clinician, antibiotic regimens can be fine-tuned which requires narrowing or broadening antibiotic therapy based on the susceptibility results (42). However, in some cases this transition to definitive therapy might not occur and the patient might still receive incorrect antibiotics to which the pathogen is resistant. This is termed as bug-drug mismatch (BDM) (Figure 2.1) (24, 25, 43).

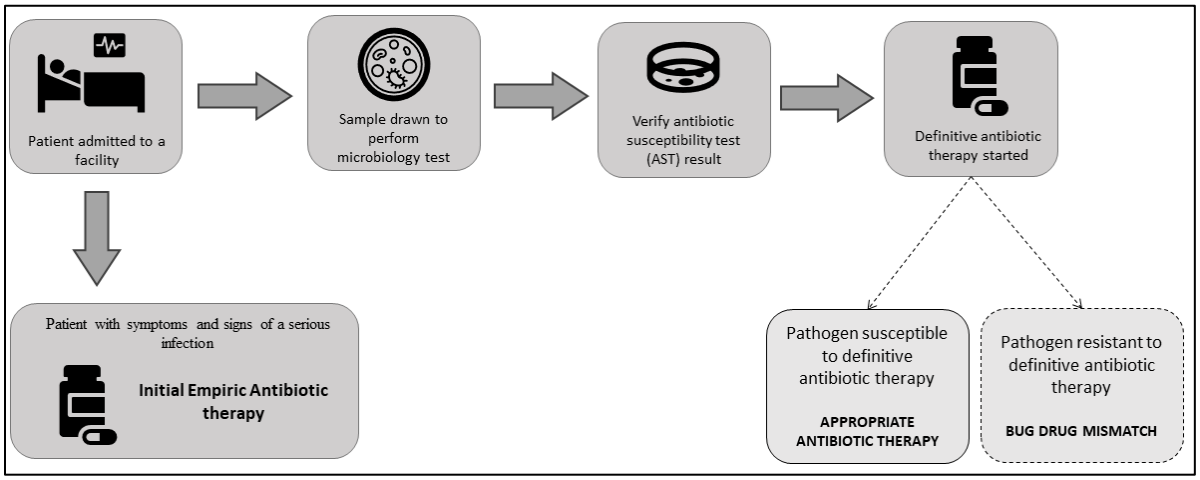

Figure 2.1. General approach to infectious disease and definition of bug-drug mismatch

2.3. Basis of Antibiotic Resistance

Antibiotic resistance (AR) occurs when a drug loses its ability to inhibit bacterial growth effectively. Several mechanisms have evolved in bacteria which confer them with antibiotic resistance. Antibiotic resistance in bacteria may be an inherent trait of the

organism that renders it naturally resistant, or it may be acquired by means of mutation in its own DNA or acquisition of resistance-conferring DNA from another source (44).

Generally, resistant microbes modify the antibiotic action in one of the following ways: Mutations that cause antibiotic resistance generally occur in three different types of genes. Among them are those encoding their transporters and regulators which reduce the level of antibiotic-disinfecting factors. Mutations in chromosome, defects in the transportation of aminoglycosides, and enzymatic inactivation are reported mechanism of resistance. These mechanisms can chemically modify the antibiotic, reprogram the metabolic pathways, decrease the ability to uptake drug, render it inactive through physical removal from the cell, or modify target site so that it is not recognized by the antibiotic. Destruction of sensitive strains by the antibiotic, allows naturally resistant strains to colonize the patient. For example, penicillin therapy destroys much of the normal oral flora and the mouth becomes colonized by penicillin-resistant organisms previously present in small numbers. A genetic mutation may occur during treatment and becomes apparent when the sensitive organisms are destroyed. Mutations in bacteria are more common with some antimicrobial agents than with others, and especially with streptomycin, rifampicin, and nalidixic acid. Certain organisms may acquire resistance as a result of the activity of phages (bacterial viruses) which incorporate a resistance gene present in one organism and when released transfer the resistance to an organism which was originally sensitive (45–47). Epidemiological factors, local antibiotic policies, patient characteristics, origin of the strains, and geographic location are among the factors contributing to highly variable resistance rates (48). Antibiotic-resistant germs, including new and emerging resistance, can spread within and between healthcare facilities. These

germs can cause infections in patients, called healthcare-associated infections (HAIs), and can spread to the community or environment (soil, water) (49, 50). The evolution and spread of antibiotic resistance challenge our continued ability to prevent and treat infectious diseases.

2.4. Increasing Trend in Antibiotic Resistance

The resistance to antibiotics is increasing at a faster pace than it can be controlled resulting in prolonged illness and greater risk of death. At the present time, about 70 percent of the bacteria that cause infections in hospitals are resistant to at least one of the drugs most commonly used for treatment (8). Some organisms are resistant to all approved antibiotics and can only are treated with experimental and potentially toxic drugs. Worrisome trends are emerging, including the discovery of new resistant pathogens, such as *Neisseria gonorrhoeae* infections (51). Other drug-resistant, community-acquired bacterial infections, such as, group A *Streptococcus* and ESBL-producing *Enterobacteriaceae* are also increasing (52). Several studies from developing countries show an alarming swing in multiple resistance among the prime enteric pathogens, such as *E. coli, Klebsiella* spp., *Salmonella* spp., *Vibrio cholerae*, and *Shigella* spp., to nearly all generally available antibiotics (53). A study estimating national trends in inpatient antibiotic use among US hospitals from 2006 – 2012 indicated significant decreases in fluoroquinolones (20%) and first- and second-generation cephalosporins (7%) usage, but these decreases were offset by significant increases in vancomycin (32%) and agents with broad-spectrum activity against gram-negative bacteria, including carbapenem (37%), third- and fourth-generation cephalosporin (12%), and β -lactam/ β -

lactamase inhibitor combination antibiotics (26%). Despite substantial reduction in fluoroquinolone use, this class remained the most commonly used antibiotic class in US hospitals in 2012 (19).

2.5. Consequences of Antibiotic Resistance

AR pathogens have become a global threat responsible for high death tolls and life-threatening infections. Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness and greater risk of death. When microbes become resistant to certain microbes, it reduces the effectiveness of treatment because patients remain infectious for longer, thus potentially spreading resistant microorganisms to others (54, 55). Consequences of these infections are aggravated enormously in volatile situations such as civil unrest, violence, famine and natural disaster (56). The World Health Organization (WHO) has warned that a post-antibiotic era will result in frequent infections and small injuries may result in death if we fail to act against antibiotic resistance (57). More than 63,000 patients from the United States of America (USA) die every year from hospital-acquired bacterial infections (58). Individuals may succumb to Multiple Drug Resistant (MDR) infections because all available drugs have failed such as examples include hospital and community MDR strains of *Mycobacterium tuberculosis*, *E. faecium*, *Enterobacter cloacae*, *K. pneumoniae*, *S. aureus*, *A. baumannii*, and *P. aeruginosa*. Every year, an estimated 25,000 patients die due to multiple drug resistance (MDR) bacterial infections(59–61). Many countries are facing the burden of nosocomial *Staphylococcus aureus* (*S. Aureus*) infections as waves of clonal dissemination. Methicillin-resistant *Staphylococcus aureus*

(MRSA) strains are rapidly spreading globally (62). Estimated costs due to multidrug-resistant bacterial infection might result in extra healthcare costs and productivity losses.

AR increases the costs of health care by billions of dollars every year (63). When infections become resistant to first-line medicines, more expensive therapies must be used. The longer duration of illness and treatment, often in hospitals, increases health-care costs and the financial burden to families and societies (64). AR jeopardizes health-care gains to society. Without effective antibiotics for care and prevention of infections, the success of treatments such as organ transplantation, cancer chemotherapy and major surgery would be compromised (65). AR also threatens health security, and damages trade and economies. The growth of global trade and travel allows resistant microorganisms to be spread rapidly to distant countries and continents. Additionally, when a patient receives treatment with antibiotics, both the causative pathogen and the normal nonpathogenic microflora in the body will be affected. The indigenous microflora makes up a complex ecological system of great importance for human health. Ideally, antibiotics should effectively kill the pathogen responsible for infections and, simultaneously, cause as little disturbance as possible to the microflora of the individual (66).

Antibiotic-resistant infections can also complicate the response to and recovery from public health emergencies. For example, during the 2009 H1N1 influenza pandemic, many patients acquired secondary bacterial infections in addition to influenza, and some of these infections were resistant to antibiotics (67). While the implications of antibiotic resistance are not yet clear for the ongoing response to COVID-19 illness, increased use of antibiotics and other antimicrobial medicines—both appropriate and

inappropriate—to address primary or secondary infections has the potential to further accelerate the emergence of antibiotic resistance (68).

The U.S. Government is responding to antibiotic resistance with a comprehensive and coordinated suite of actions implemented by a diverse set of agencies using a One Health approach. The National Strategy for Combating Antibiotic-Resistant Bacteria (CARB) has laid out five goals to reduce the incidence and impact of antibiotic-resistant infections for the years 2020-2025. Several drug susceptibility surveillance systems such as the Alliance for the Prudent Use of Antibiotics, the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS), the National Antimicrobial Resistance Monitoring System (NARMS) and the CDC National Healthcare Safety Network (NHSN) was established to help to assess the current status of resistance in a location (5, 69–71). Inappropriate and irrational use of antibiotics provide favorable conditions for resistant microorganisms to emerge, spread and persist.

2.6.Complex Determinants of Inappropriate Antibiotic Use

Antimicrobial agents are some of the most widely, and often injudiciously, used therapeutic drugs worldwide. For instance, in the United States, 80 million prescriptions of antibiotics for human use were filled and this equals 12,500 tons in one year (72). Important considerations when prescribing antimicrobial therapy include obtaining an accurate diagnosis of infection; understanding the difference between empiric and definitive therapy; identifying opportunities to switch to narrow-spectrum, cost-effective oral agents for the shortest duration necessary; understanding drug characteristics that are peculiar to antimicrobial agents (such as pharmacodynamics and efficacy at the site of infection); accounting for host characteristics that influence antimicrobial activity; and in

turn, recognizing the adverse effects of antimicrobial agents on the host (73). Data show a direct correlation between the use of antibiotics and resistance. Countries with a higher consumption of antibiotics show higher rates of resistance (74).

It has been a standard practice for most of the pharmaceutical companies to distribute antibiotics that may no longer be effective or lack regulatory approval. Although, increased antibiotic use result in a positive association with a higher prevalence of resistant microorganisms, while reduced antibiotic use indicate lower resistance rates (75). There is clear evidence that patients historically treated with antibiotics are more likely to have antibiotic resistance (76). Further, re-administration of antibiotics from the initial cycle accelerates resistance mechanisms. Antibiotics encourage selective pressure for bacteria to evolve when administered frequently or irrationally (77).

Inappropriate use of antibiotics in humans and agriculture is one of the drivers of the emergence of antimicrobial resistance (78, 79). The prevalence of penicillin-resistant pneumococci, macrolide-resistant *Streptococcus pneumoniae* and *S. pyogenes* strongly correlates with total antibiotic use in outpatients. Such inappropriate use is the result of complex interactions between demand for and supply of antibiotics. Health professionals who prescribe or dispense antibiotics, when motivated by financial incentives, can induce demand through the unnecessary use of antibiotics (80).

Several cross-sectional studies have evaluated factors contributing to antibiotic misuse in children (81–84). These studies found that insufficient parental knowledge and negative attitudes were among the most important factors contributing to inappropriate antibiotic prescription. Low educational level, being a single parent, having low income,

and being without experience in recurrent infections were significantly related to inadequate knowledge and negative attitude toward antibiotic use in children.

2.7.Consequences of Bug-Drug Mismatch

In addition to antibiotic overuse, Bug-Drug Mismatch (BDM) is also an important and modifiable contributor to inappropriate antibiotic use which is one of the drivers of emergence of AR and is a problem in all health care settings (85). Incorrectly prescribed antibiotics have questionable therapeutic benefit and expose patients to potential complications of antibiotic therapy. Subinhibitory and subtherapeutic antibiotic concentrations can promote the development of antibiotic resistance by supporting genetic alterations which promote antibiotic resistance and spread (86). Several studies have evaluated the association between appropriate antibiotic therapy and mortality among bacteremic patients (16, 87–90). The appropriateness of antibiotic therapy should be assessed on a case-by-case basis. Therapy should be considered to be appropriate if the regimen exhibits *in vitro* activity against the isolated pathogen. Patients receiving incorrectly prescribed antibiotics have questionable therapeutic benefit and were reported to have significantly higher mortality rate, length of hospitalization, hospital readmission rates and costs (23, 91–94).

2.8.Growing Threat of AR in Children

AR is a global public health threat that continues to escalate and impact all populations, however, until recently, the trend in drug resistant infection in children has gone relatively uncharacterized (95). Studies regarding CA-MRSA in U.S. children generally highlight the rapid increase in infections from the mid-1990s until 2005–2006,

with a subsequent decrease in infection rates thereafter (96) . However, there is significant geographic variation, and while both pediatric HA-MRSA and CA-MRSA rates have mostly stabilized, some regions have noted continued increases in CA-MRSA infection (97, 98). Trimethoprim-sulfamethoxazole (TMP/SMX) and clindamycin are often used in the treatment of CA-MRSA; and while resistance to TMP/SMX has remained relatively uncommon, clindamycin resistance in both CA-MRSA and methicillin-sensitive *S. aureus (*MSSA) has increased over the past decade. A recent study from the U.S. Military Health System found CA-MRSA clindamycin resistance increased from 9.3% in 2005 to 16.7% in 2014 (99). Similar increases in MSSA clindamycin resistance have been reported (100). In the U.S., current resistance to macrolides has been estimated at approximately 5%, a two-fold increase compared to 1990s. The clinical significance of this resistance has become apparent, as some children treated with macrolides for *S. pyogenes* pharyngitis developed acute rheumatic fever(101, 102). Antibiotic resistance in *Enterococcus* species (*E. faecalis and E. faecium*) became a significant problem in healthcare settings during the 1980s, when the organisms began displaying high level resistance to vancomycin. While VRE remain stable residents of adult intensive care units (ICUs), these resistant organisms have increased in pediatric inpatient settings. A study of VRE in U.S. children described VRE rates of 53 cases per million in 1997 which increased to 120 cases per million by 2012. The majority of affected children had a history of prolonged healthcare and antibiotic exposures (103).

Pediatric-focused antibiotic stewardship programs (ASP) are necessary because of their overall high levels of antibiotic exposure and immature immune system. In addition to these factors, the type of facility could also be a factor in the trend in resistance,

especially in Hospital Acquired Infections (HAI)(11). However, very little is known about the difference in the emerging trend in resistance pattern between children treated in pediatric and blended facilities. Estimating the difference in the trends in resistance is essential to formulate strategies and interventions to prescribe appropriate antibiotics and improve the outcome of individual patients. Definitive inappropriate use of antibiotics varied depending on the type of care setting as well as between children and adults (17, 18). Pediatric facilities have been found to vary substantially in their use of antibiotics among children(15). Recent research also shows that children admitted to non-pediatric emergency departments were more likely to receive inappropriate antibiotics(104). A comprehensive analysis estimating IAAT prescriptions between different patient population and care setting is critical to understand the actual situation of antibiotic use. However, to our knowledge, there has not been a study of IAAT that considers the influence of age and the type of healthcare setting. Antimicrobial adverse effects have been found to differ between children and adults (105, 106). Given the disparity within the age of the patient and the type of facility, it is necessary to synthesize the best available evidence to be able to predict patient outcomes such as the mortality rate, the length of hospitalization and hospital readmission in these settings. Data derived from EHRs loaded into multi-institutional data warehouses provide a powerful resource for addressing these issues.

2.9. Antibiotic Stewardship Program (ASP) Initiatives

One important strategy to combat antibiotic resistance is the use of institutional Antibiotic Stewardship Programs (ASPs). ASPs are programs that work to promote the appropriate use of antibiotics and to decrease the spread of resistant organisms. They are

instituted by the hospital, and they often involve a multidisciplinary team that reviews antibiotic use and advises providers on how to use antibiotics more effectively (107). ASPs have been shown to be very effective in helping to optimize antibiotic use and reduce healthcare costs. Studies have demonstrated that institutional implementation of ASPs has led to a decrease in patients being infected with both C. diff and even VRE (108). Additionally, ASPs have led to decreased costs associated with treating patients requiring antibiotics. This is important to consider as the price of many antibiotics has greatly increased. ASPs have shown great promise but implementation is limiting their effect. Currently, 79% of university hospitals have ASPs but only 40% of community hospitals have designated ASPs. ASPs have been shown to make a difference but their effectiveness will be limited until they become more broadly applied (109).

Antibiotic resistance and its widespread implications present predicament to healthcare. Access to emerging trends in antibiotic resistance and patterns of appropriate therapy for adults and pediatric patients within pediatric and blended facilities is critical in expanding antibiotic stewardship efforts in these settings. This would likely improve patient outcomes while limiting the risk of drug resistance by helping clinicians determine how to apply newer diagnostic modalities and therapeutic options.

2.10. Machine Learning in Health Care

Machine learning has progressed dramatically over the past two decades, from laboratory curiosity to a practical technology in widespread commercial use. Machine-learning algorithms vary greatly, in part by the way in which they represent candidate programs (e.g., decision trees, mathematical functions, and general programming

languages) and in part by the way in which they search through this space of programs (e.g., optimization algorithms) (110). The most widely used machine-learning methods are supervised, unsupervised, semi-supervised learning and reinforcement learning methods. In supervised learning, input data is called training data and has a known label. The model establishes a learning process, compares the predicted results with the actual results of the training data and continuously adjusts the predictive model until the predicted results of the model reach an expected accuracy, such as classification and regression problems. Common algorithms include decision trees, Bayesian classification, least squares regression, logistic regression, support vector machines, neural networks, and so on (111). In unsupervised learning, input data is not labeled and does not have a known result. The model is prepared by deducing structures present in the input data through a mathematical process to systematically reduce redundancy or to organize data by similarity or to infer the intrinsic links of data, such as clustering and association rule learning. Common algorithms include independent component analysis, K-Means and A-priori algorithms (112). In semi-supervised learning, input data is a mixture of labeled and un-labelled data. Common algorithms include graph theory inference algorithms and Laplacian support vector machines. In reinforcement learning, input data is fed back to the model, emphasizing how to act based on the environment to maximize the expected benefits (113).

Since the 1980s, deep learning and biomedical data have been coevolving and feeding each other. The breadth, complexity, and rapidly expanding size of biomedical data have stimulated the development of novel deep learning methods, and application of these methods to biomedical data have led to scientific discoveries and practical

solutions. The ability of machine learning to extract information from data, paired with the centrality of data in healthcare, makes research in machine learning for healthcare crucial (114). Interest in machine learning for healthcare has grown immensely, including work in diagnosing diabetic retinopathy, detecting lymph node metastases from breast pathology, autism subtyping by clustering comorbidities, large- scale phenotyping from observational data, predicting patient risk of sepsis, predicting a patient's likelihood of readmission to the hospital, and predicting the need for end of life care (115–120). The advent of large-scale data sets provided by next-generation sequencing and electronic health records (EHR's) make applying machine learning to the study and treatment of AR possible. To date, it has been used for antimicrobial susceptibility genotype/phenotype prediction, development of AR clinical decision rules, novel antimicrobial agent discovery and antimicrobial therapy optimization (121, 122).

One pivotal impediment in ML relates to the black box nature, or opacity, of many machine learning algorithms (123). Especially in critical use cases that include clinical decision making, there is some hesitation in the deployment of such models because the cost of model misclassification is potentially high in healthcare. Historically, there has been a trade-off between interpretable machine learning models and performance (precision, recall, F-Score, AUC, etc.) of the prediction models. More interpretable models like regression models and decision trees often perform less well on many prediction tasks compared to less interpretable models like gradient boosting, deep learning models, and others(124). Researchers and scientists have had to balance the desire for the most highly performing model to that which is adequately interpretable.

However, recently, many ML based clinical decision support systems (CDSS) which are computer-based programs where the characteristics of an individual patient are analyzed by the ML algorithms to present patient-specific assessments or recommendations to the clinician towards a decision (125). The first FDA approval for an autonomous AI system took place in 2018 with IDx, a ML system used to detect diabetic retinopathy in retinal fundus photographs (126). Although there are still some limitations with the interpretability of ML models, the utility of ML models in the implementation of CDSS tools in healthcare are advantageous and must be explored. However, currently there are no ML studies on predicting antibiotic use or BDM occurrence.

In this study, in addition to exploring the trends of AR, prevalence and risk factors of BDM, we also predicted BDM occurrence using ML models and compared the predictive performance with a reference LR model. These findings are critical in tailoring antibiotic stewardship efforts to improving appropriate antibiotic prescribing and to ultimately reduce AR.

CHAPTER 3

VARIATION IN ANTIBIOTIC RESISTANCE PATTERNS FOR CHILDREN AND ADULTS TREATED AT 166 NON-AFFILIATED US FACILITIES

3.1. Introduction

The emergence of antibiotic-resistant (AR) bacteria endangers the efficacy of antibiotics and is a global public health crisis (127, 128). The Centers for Disease Control and Prevention (CDC) estimates 2.8 million people in the U.S. are infected each year with bacteria resistant to antibiotics with an average of 35,000 deaths (3). AR infections cause significant morbidity and mortality worldwide and could reach up to 10 million deaths by 2050 (129, 130). AR infections can double the duration of hospital stays, increase mortality rate, prolong treatment and increase healthcare costs (41, 131). Estimates suggest AR infections contribute $35 billion to health-care costs per year in the US (132).

The CDC and World Health Organization (WHO) provide prioritized lists of AR bacteria based on level of concern to human health (3, 133). The ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter* spp.) are considered to be the most emergent AR threats (134, 135). Several US studies show an alarming increase in resistance among pathogenic gram-negative (GN) bacilli, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli, Proteus mirabilis, Serratia*

marcescens, Haemophilus spp., *Klebsiella* spp., *Salmonella* spp., *Citrobacter* spp., *Enterobacter* spp., and *Shigella* spp. (59, 136–143). Gram-positive bacteria cause serious and difficult to treat infections, exacerbated by marked increases in antibiotic resistance among these bacteria, most notably methicillin resistance in *Staphylococcus aureus* (MRSA), decreased susceptibility to penicillin in *Streptococcus pneumoniae* and vancomycin resistant *Enterococci* (VRE) (144–146). Tracking emerging patterns of antibiotic resistance allows providers to precisely tailor antibiotic therapy and prevent the spread of existing AR.

Drug susceptibility surveillance systems such as the Alliance for the Prudent Use of Antibiotics, the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS), the National Antimicrobial Resistance Monitoring System (NARMS) and the CDC National Healthcare Safety Network (NHSN) help to assess the current status of resistance in a location (5, 69–71). These resources do not provide granular information at the facility level. Institution specific antibiograms are generated by health-care facilities to report, track and benchmark AR bacteria. They are often generated by a multidisciplinary team that annually review the resistance patterns to inform appropriate use of antibiotics and to decrease the spread of resistant organisms (147). These antibiograms do not generally include patient demographics such as gender, race or age.

Until recently, trends in drug resistant infections in children have been relatively uncharacterized. Isolates from children have different selective pressure due to their evolving immune system, increased risk of adverse events or overall antimicrobial exposure (95, 105, 106, 148). A recent study found a 700-percent surge in pediatric infections caused by the enteric pathogens resistant to multiple antibiotics in the US over

a period of 8 years (149). For example, clindamycin resistance among isolates from children in both MRSA and methicillin-susceptible *S. aureus* (MSSA) has increased from 9.3% in 2005 to 16.7% in 2014 (150). VRE isolates from children increased from 53 cases per million in 1997 to 120 cases per million in 2012 in US (103). The type of facility (standalone pediatric or blended facilities caring for adults and children) could also be a factor for different resistance patterns in children, especially in Hospital Acquired Infections (HAI) (11). Pediatric facilities have been found to vary substantially in their use of antibiotics (15). AR patterns for priority pathogens have not been compared between children and adults nor between types of facility. This would inform pediatric care-setting focused antibiotic stewardship programs (ASP).

Data derived from EHRs loaded into multi-institutional data warehouses provide a powerful resource for examining these issues. One such data resource, Cerner Health Facts™ (HF), contains micro-susceptibility test results from multiple sites (151). The objective of this study is to compare the trends in resistance for the priority bacterial pathogens between children and adults as well as among children treated in primarily pediatric facilities and blended facilities.

3.2. Methods

3.2.1. Data Source

We derived the study data from Cerner Health Facts database (Kansas City, MO, USA) populated by the daily extraction of discrete EHR data from participating organizations. HF data is de-identified in a manner compliant with US Health Insurance Portability and Accountability Act (HIPAA) standards. In the 2018 version of the HF,

416 facilities associated with 84 nonaffiliated health systems have contributed 5 million distinct micro-susceptibility encounter data from 3 million patients to HF at intervals from January 2000 through 2017. HF includes microbiology results, patient demographics, diagnoses, medication orders, other laboratory tests and clinical procedures. The Children's Mercy Institutional Review Board has designated research with HF data as "non-human subjects research."

3.2.2. Data Definition

The efficacy of the antibiotics against the pathogens is interpreted as resistant(R) if the isolates are not inhibited by the recommended dosage of antibiotic and there is a bacterial growth in the presence of the antibiotic; susceptible (S) if the isolates are inhibited by the recommended dosage of antibiotic; and intermediate (I) if there is limited growth in the presence of dilute antibiotics (152). The calculation of antimicrobial resistance (proportion of R relative of the total) is dependent on two prerequisites: the data should only consist of first isolates (the isolate of a bacterial species found first in a patient per encounter) and a minimum required number of 30 isolates per year for every group (153, 154).

3.2.3. Data Validation

Every encounter in HF is associated with a health system ID and a contributing facility within the health system. Children's Mercy Hospital (CMH) is a contributor to HF. In order to test the reliability of HF data, we extracted the 2017 CMH antimicrobial susceptibility data using the health system ID in HF and compared it with the CMH 2017 antibiogram (155) (Table 3.1). We evaluated the reliability of the data using a single-

measurement, absolute-agreement, 2-way mixed-effects intra-class correlation (ICC) method (156).

Table 3.1. HF data validation with CMH antibiogram.

GRAM-NEGATIVE ANTIBIOGRAM															
Source	**Amikacin**	**Amox/clav**	**Amp/Sulbactam**	**Ampicillin**	**Cefazolin**	**Cefepime**	**Ceftazidime**	**Ceftriaxone**	**Ciprofloxacin**	**Gentamicin**	**Meropenem**	**Nitrofurantoin**	**Pip/tazo**	**Tobramycin**	**Trimeth/Sulfa**
A.baumanni															
CMH			100				82	33	94	94	100			94	97
HF			100				86	36	93	86	100			100	100
C.freundii															
CMH	100						96	96	96	92	100		96	92	88
HF							95	95	100	100	100				86
E.aerogenes															
CMH	97					100	84	84	100	92	100		24	92	88
HF	100					100	73	77	100	95	100				100
E.cloacae															
CMH	100					99	90	90	99	100	98		43	100	94
HF						97	95	95	100	100	100				93
E.coli															
CMH	100	86	39	51	88	96	95	96	91	94	99	97	97	94	76
HF	100	100		54	92	99	99	99	93	95	100	97	97	11	75
K.oxytoca															
CMH	100	96			61	97	97	97	100	97	100		88	97	93
HF					67	100	100	100	100	100	100	88			92
K.pneumoniae															
CMH	99	96			92	96	96	96	96	94	100	96	28	94	90
HF					96	100	100	100	99	99	100	21			90
P.aeruginosa															
CMH	99					96	96		95	91	97	95		94	
HF	46					60	98		84	67	84			75	
P.mirabilis															
CMH	100	98		93	98	100	100	100	96	95	100	0	100	95	89
HF				94	99	100	100		97	95		0	100		89
S.marcesces															
CMH	100					96	96	94	100	100	100			86	100
HF						100	100	100	100	100	100				100

GRAM-POSITIVE ANTIBIOGRAM															
Source	**Ampicillin**	**Cefotaxime**	**Ciprofloxacin**	**Clindamycin**	**Erythromycin**	**Gentamicin**	**Linezolid**	**Meropenem**	**Nitrofurantoin**	**Oxacillin**	**Penicillin**	**Rifampin**	**Tetracycine**	**Trimeth/Sulfa**	**Vancomycin**
MRSA															
CMH				81	48	99	100		100	0	0	100	96	96	100
HF				71	15	98	100		100	0	0	99	98	94	100
MSSA															
CMH				79	63	100	100		100	100	0	100	95	96	100
HF				77	63	99	99		100	100	0	100	95	97	100
S.epidermis															
CMH			73	52	33	89	100		100	30	0	98	87	68	100
HF				44	29	89	100		100	34	0	97	80	59	100

Note: Health Facts (HF) data and Children's Mercy Hospital (CMH) 2017 antibiogram; MSSA- Methicillin Susceptible *Staphylococcus aureus*; MRSA- Methicillin Resistant *Staphylococcus aureus*;

3.2.4. Pathogen-Antibiotic Combinations

Each record in the dataset includes the pathogen, susceptibility test results and the time stamp of the test result verification. In order to minimize the number of pathogens, we selected relevant pathogens based on the CDC report on greatest AR threats and the WHO list of global priority antibiotic resistant bacteria (3, 133). There are 22 such pathogens: *Acinetobacter baumannii, Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Enterococcus faecium, Escherichia coli, Haemophilus influenzae, Klebsiella oxytoca, Klebsiella pneumoniae,* MRSA, Methicillin-susceptible *Staphylococcus aureus* (MSSA), *Proteus mirabilis, Pseudomonas aeruginosa, Salmonella* spp., *Serratia marcescens, Shigella* spp., *Staphylococcus* Coag Neg spp. (CoNS), *Streptococcus* Group A, *Streptococcus* Group B, *Streptococcus pneumoniae, Streptococcus viridans* and VRE. In order to focus on clinically relevant antibiotics, we included Clinical and Laboratory Standards Institute (CLSI) recommended antimicrobial agents approved by the US Food and Drug administration for clinical use that are considered for routine testing and reporting by microbiology laboratories in the U.S. (157). There are 41 clinically relevant antibiotics for those 22 pathogens (Table 3.2). Antibiotics primarily used to treat urinary tract infections are only considered for isolates whose source of infection is specifically urinary.

Table 3.2. Pathogen-Antibiotic combinations

Antibiotic	MSSA	CoNS	MRSA	Strep	Entero	GNR	Pseudo
Amikacin						778,611	77,477
Amoxicillin-Clavulanate						197,415	
Ampicillin				21,460	19,036	821,228	
Ampicillin-Sulbactam	42,244				143	847,299	
Aztreonam						462,059	30,671
Cefazolin	58,772	17,078				808,011	
Cefepime				7,196		880,360	83,460
Cefotaxime				16,830			
Cefotetan						53,955	
Ceftazidime						719,160	72,043
Ceftriaxone	24,248	12,288		29,105		990,847	
Cefuroxime	879	982		2,448		244,989	
Ciprofloxacin					8,062	963,469	90,321
Clarithromycin	2,769						
Clindamycin	199,368	63,062	103,188	36,073			
Dalfopristin-Quinupristin	10,519		7,787		815		
Daptomycin	65,242	21,662	34,324	1,703	6,707		
Doripenem						40,965	4,666
Doxycycline							
Ertapenem						528,311	
Gentamicin	187,678	80,664				1,054,345	95,205
Imipenem	10,603			518	54	473,624	50,659
Levofloxacin	156,326	74,092		37,585	9,180	851,512	61,233
Linezolid	146,544	59,448	90,735	24,145	16,685		
Meropenem	7,331			5,725	61	671,669	67,540
Moxifloxacin	71,526	23,857		7,078		43,695	
Nitrofurantoin					11,354	860,473	
Oxacillin	170,135						
Penicillin				43,616	14,417		
Piperacillin-tazobactam	1,636				24	871,241	79,811
Rifampin	169,937	73,547					
Tetracycline					10,123		
Tigecycline	64,202		41,200	7,179	4,731	241,147	
Tobramycin						875,088	86,545
Trim/Sulf	209,141	48,727	104,987	12,499		1,044,670	
Vancomycin	178,338	73,949	94,615	37,298	4,435		

Note: MSSA- Methicillin Susceptible *Staphylococcus aureus*; MRSA- Methicillin Resistant *Staphylococcus aureus*; CoNS – Coag Negative *Staphyloccocus*; Strep –

S.pyogenes, S.agalactiae, S.pneumoniae, S.viridans; Enterococci – *E.faecium*, VRE; Pseudo – *P.aeruginosa*; GNR – Gram negative rod organisms (*C.freundii, E.aerogenes, E.cloacae, E.coli, H.influenzae, K.oxytoca, K.pneumoniae, P.mirabilis, Salmonella spp, S.Marcescens and Shigella spp*).
Excluded intrinsically resistant combinations:
[a] Pathogens (C.freundii, E.aerogenes, E.cloacae, S.marcescens) - Antibiotics (Ampicillin, Ampicillin-Sulbactam, Amoxicillin-Clavulanate, Cefazolin);
[b] Pathogens (K.oxytoca, K.pneumoniae) – Ampicillin;
[c] Pathogens (P.mirabilis, S.marcescens) -Nitrofurantoin

3.2.5. Study Design

We conducted a retrospective study of encounters with the 22 priority pathogens with microbiology susceptibility results for the FDA recommended and clinically relevant antibiotics between the years 2012 to 2017 (Figure 3.1). *S. aureus* isolates were classified as MRSA if oxacillin/methicillin resistant and MSSA if oxacillin/methicillin susceptible. We included encounters of the pathogens which reported valid susceptible, intermediate, or resistant results with a valid date stamp. Facilities consistently reporting the microbiology susceptibility every year between the years 2012 to 2017 were included (166 facilities) while 241 facilities with inconsistent data were excluded. Facilities where the mean age of patients is less than eighteen were identified as likely pediatric facilities and facilities treating both adults and children were identified as blended facilities. We separated the data cohort into four groups: encounters of the isolates from children (Age <18) (Group I); and adults (Age >18) (Group II); isolates of children from pediatric facilities (Group III) and isolates of children from blended facilities (Group IV). Pathogen-antibiotic combinations with minimum required number of 30 isolates per year were included in every group (Figure 3.1).

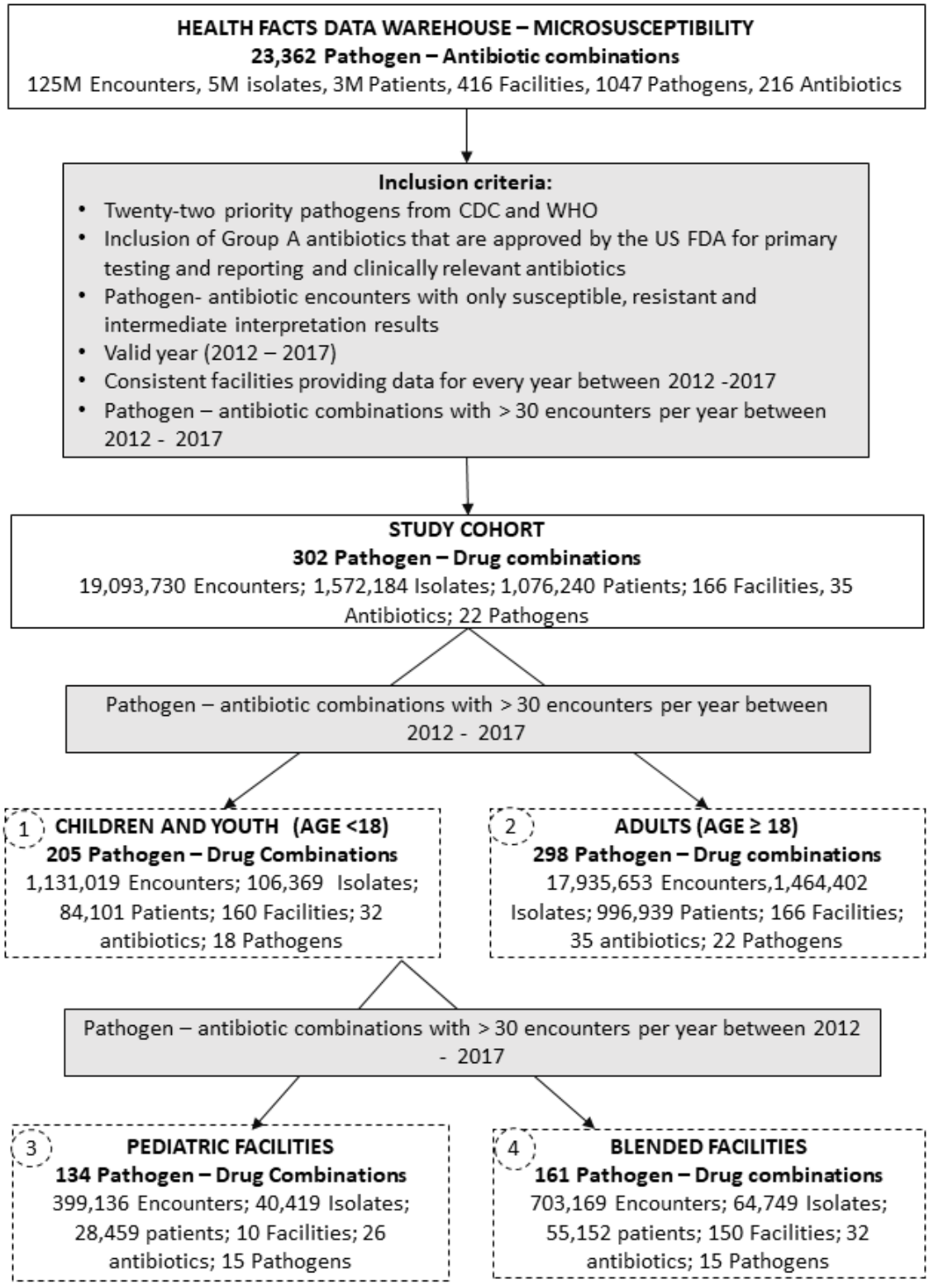

Figure 3.1. Data extraction and study design.

3.2.6. Analysis

We examined the resistant percentage of each pathogen-antibiotic pair individually and in relation to the four cohorts. We calculated the slope coefficient for the trend in proportion of resistance of every pathogen-antibiotic combination over the years of 2012 to 2017 by utilizing linear regression. The data is installed in Microsoft (Redmond, WA) Azure and queries are performed with R Studio version 1.1.453 with R version 3.6.1. An analysis that we refer to as the Multiple Categorical Slope (MCS) was performed for the total cohort and for all the four groups to identify significant antibiotic-resistant-pathogens which are increased/decreased over the years. In the MCS plot, the calculated slopes of the pairs are plotted on the Y-axis and similar to a Manhattan plot, the X-axis of the plot shows antibiotics as dots organized by pathogens, in different colored blocks. The pairs which increased during the period evaluated are indicated above the upper limit (95^{th} percentile value of the slope) horizonal line while the pairs which decreased are indicated below the baseline lower limit (5^{th} percentile value of the slope). We compared the significance of the difference in the slope between children vs adult (Group I vs II) as well as children in pediatric facilities vs blended facilities (Group III vs IV) through the Comparison-MCS plot. In the C-MCS plot, the effect of the interaction term [group X year] are plotted for every pathogen-antibiotic pair. The significance of the interaction term was tested to determine pathogen-antibiotic pairs with unequal slopes that represent a different pattern in the trend in resistance between children and adults as well as between children in pediatric facilities and children in blended facilities.

3.3. Results

3.3.1. Characteristics of Data

The reliability of the data evaluated using ICC indicate that the agreement of the data between HF and the CMH antibiogram is considered to be excellent (ICC = 0.84 [95% CI: 0.77 – 0.88], After excluding outliers: ICC=0.984 [95% CI: 0.977 – 0.99]).

The 2018 version of the HF microbiology susceptibility data includes 125 million susceptibility results evaluated from 1047 pathogens screened for resistance to 216 antimicrobials resulting in 23,362 unique pathogen-antibiotic combinations. Isolate samples were reported from 550 distinct body source sites. Urinary tract isolates constituted 63% of all isolates. The majority of the susceptibility tests used minimal inhibitory concentration (MIC) or Kirby- Bauer (KB) method. Inclusion of 22 priority pathogens and clinically relevant antibiotics resulted in 302 pathogen-antibiotic combinations yielding 19 million encounters in the study cohort. This cohort consists of 1.5 million isolates identified from 1 million patients associated with 166 U.S. facilities. Most (63%) facilities were non-teaching institutions, and the majority (80%) were located in urban environments. More than two-thirds (68%) had fewer than 200 beds, 28% had 200-500 beds and 4% had more than 500 beds.

There were 84,101 patients in the cohort younger than 18 (13% of the HF cohort) whose encounters were segregated into Group I (children), the remaining encounters in Group II (adults). Group I includes encounters from 160 facilities with 10 pediatric facilities. Those encounters were separated into Group III (pediatric facilities) while the remaining encounters are Group IV (blended facilities). Data characteristics of these groups are summarized in Figure 3.1.

3.3.2. Baseline Resistance

Within the total study cohort, the 22 priority pathogens with the highest percentage of resistance to the clinically relevant antibiotics are shown in Figure 3.2 (number of isolates tested; % resistant). Among the pathogens with highest total level of resistance, *Streptococcus* Group B had the highest resistance to clindamycin (22,252; 52.79%).

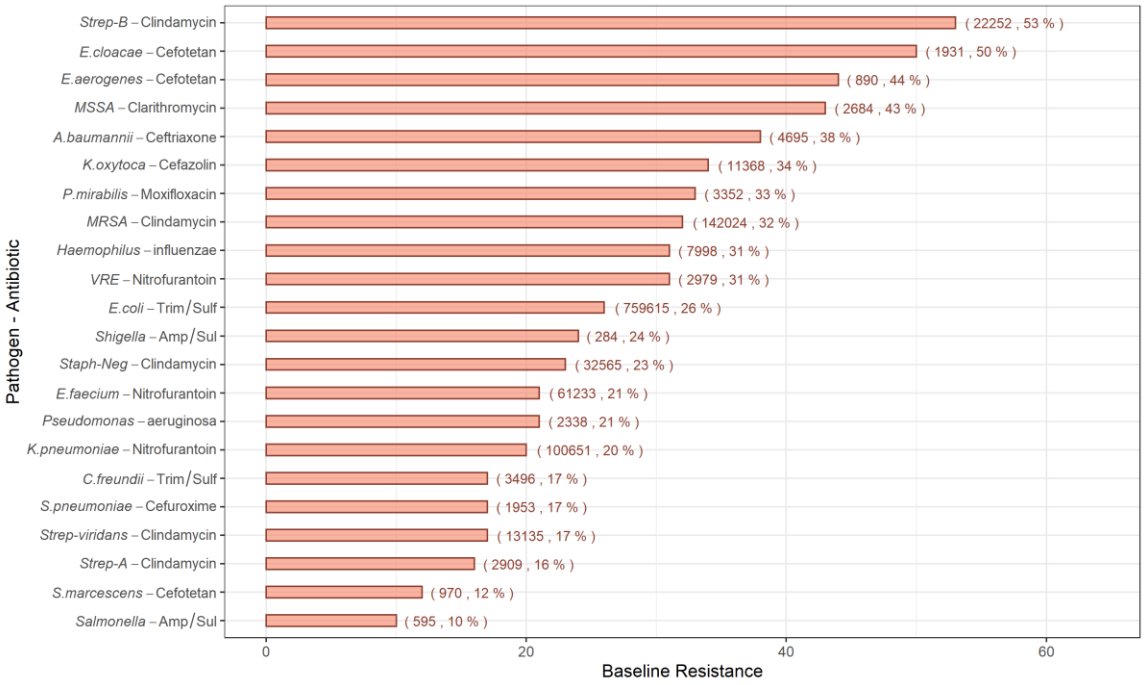

Figure 3.2. Baseline resistance of the study cohort. (Total no. of resistant encounters, Resistance %)

We compared resistance patterns based on age group (Figures 3.3A and 3.3.B) and care setting (Figures 3.3C and 3.3D). The overall difference in the proportion of resistant isolates was higher in adults when compared to children (Figures 3.3A and

3.3B). For example, isolates from adults had a higher proportion of ciprofloxacin resistant *A. baumannii* (38% Vs 6%, p<0.0001) while isolates from children had a higher proportion of amikacin resistant *P. aeruginosa* isolates (17% vs 4%, p<0.0001). Children in pediatric facilities had a higher proportion of resistant isolates when compared to blended facilities (Figure 1.3C and D). For example, isolates from children in pediatric facilities had a higher proportion of ceftriaxone resistant *E. aerogenes* compared to those treated in blended facilities (21% vs 4%, p<0.0001) while isolates from children in blended facilities had a higher proportion of penicillin resistant *S. pneumoniae* (18% Vs 2%, p<0.0001).

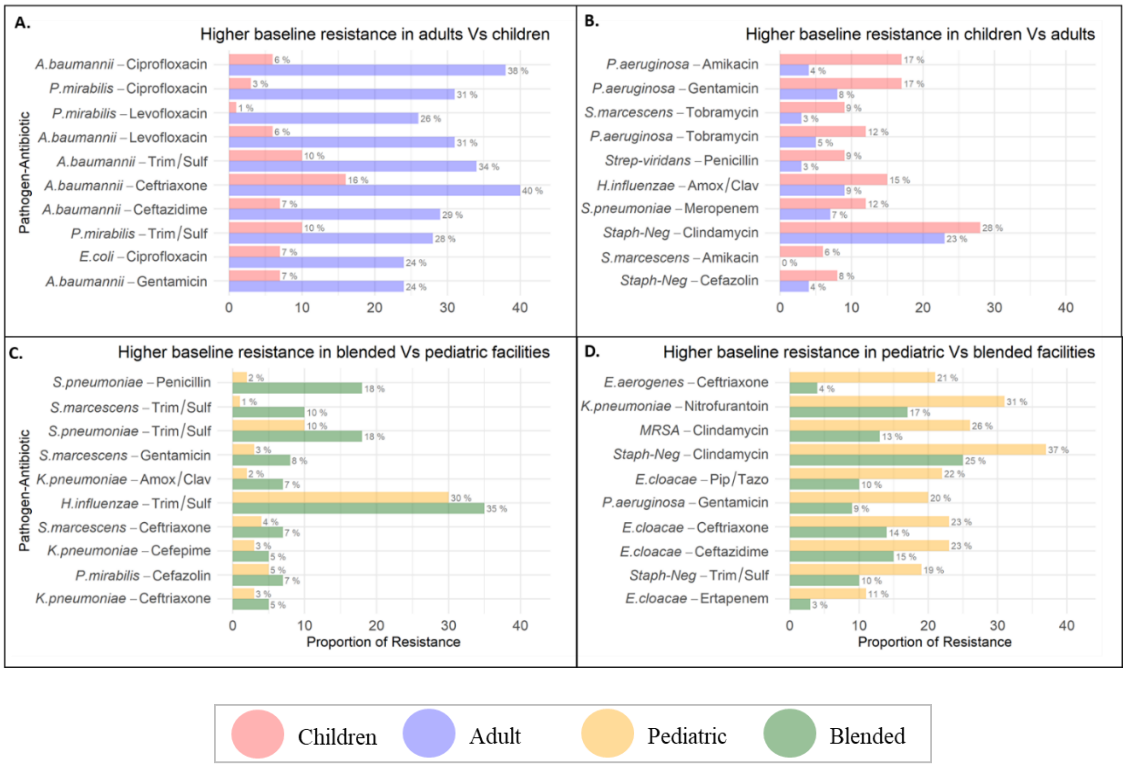

Figure 3.3. Difference in level of resistance between subgroups. Higher baseline resistance in isolates from: (A) Adults when compared to children. (B) Children when compared to adults. (C) Children in blended facilities when compared to pediatric facilities (D) Children in pediatric facilities when compared to blended facilities

3.3.3. Trend in Resistance

The MCS plot of the study cohort is shown in Figure 3.4A. The predominant pair was ciprofloxacin resistant *Shigella* sp. which increased from 1.6% to 8% between 2012-2017 (slope = 1.17, R^2=0.972, p=0.003) and ceftazidime resistant *A. baumanii* which decreased from 34% to 24% (slope = -6.24, R^2=0.981, p=0.004). The positive and negative trends of other statistically significant pairs are depicted in Figure 3.4B.

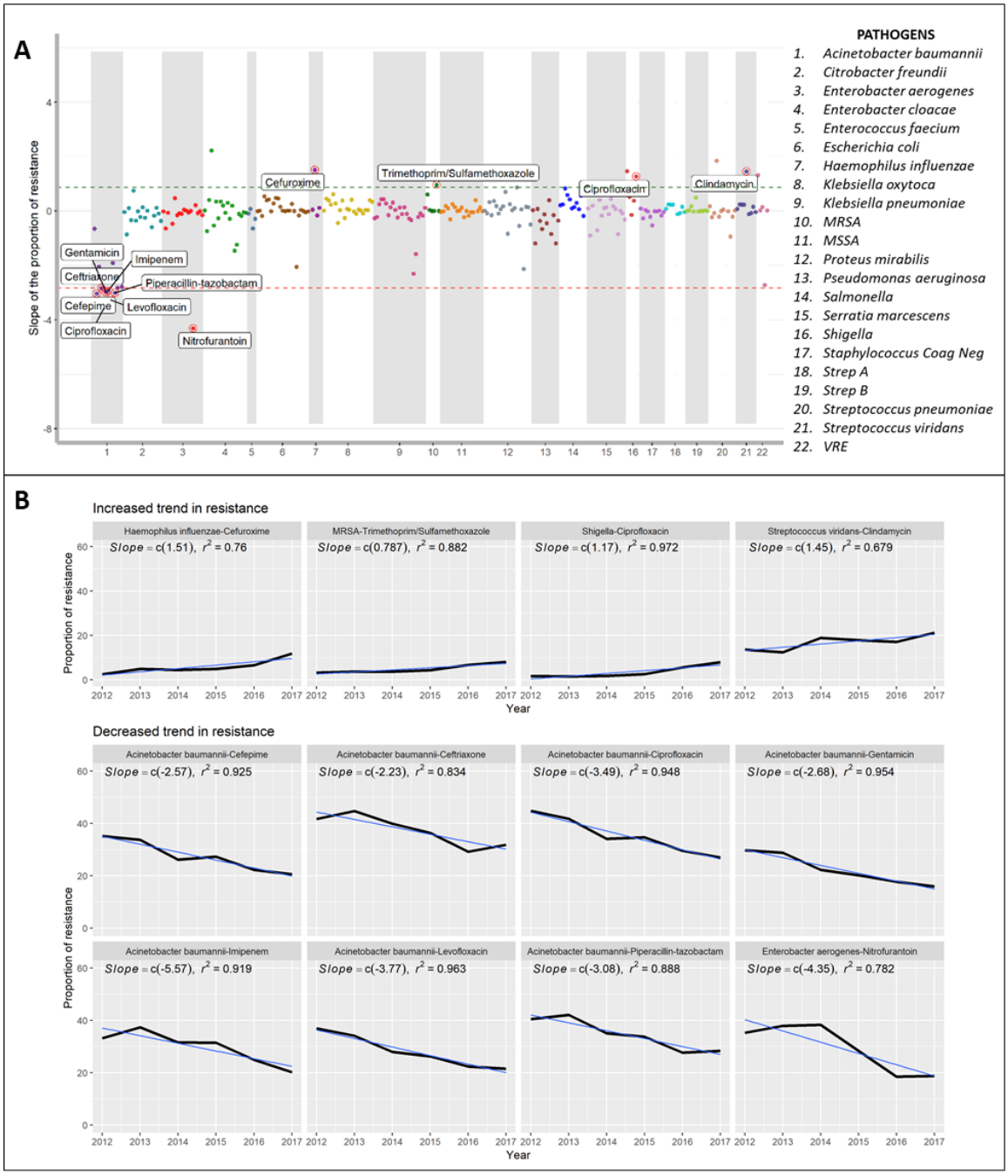

Figure 3.4. MCS (Multiple Categorical Slope) Plot of the study cohort. (A) MCS plot: Calculated slopes of the antibiotic-resistant-pathogen pairs are plotted on the Y-axis, the X-axis of the plot shows antibiotics as dots organized by pathogens (listed to the right), in different colored blocks. Statistically significant pairs which increased between 2012 – 2017 are highlighted above the upper limit (95th percentile value of the slope) horizonal line while the pairs which decreased are highlighted below the baseline lower limit (5th percentile value of the slope). (B) Patterns of increased/decreased trend in resistance of statistically significant antibiotic-resistant-pathogens

The pathogen-antibiotic combinations with a significant positive and negative trend for all the four groups are shown in Figure 3.5. Among isolates from adults, cefuroxime resistant *H. influenzae* increased from 1.4% to 8% (slope = 1.9, R^2=0.945, p=0.02), while ceftazidime resistant *A. baumanii* decreased from 36.1% to 25.3% (slope = -6.81, R^2=0.972, p=0.004) (Figure 3.6). Among isolates from children, clindamycin resistant MRSA increased from 15.5% to 24.2% (slope =1.86, R^2=0.992, p=0.0007) while nitrofurantoin resistant *E. aerogenes* decreased from 37.1% to 13.3% (slope = -5.19, R^2=0.959, p=0.009) (Figure 3.7).

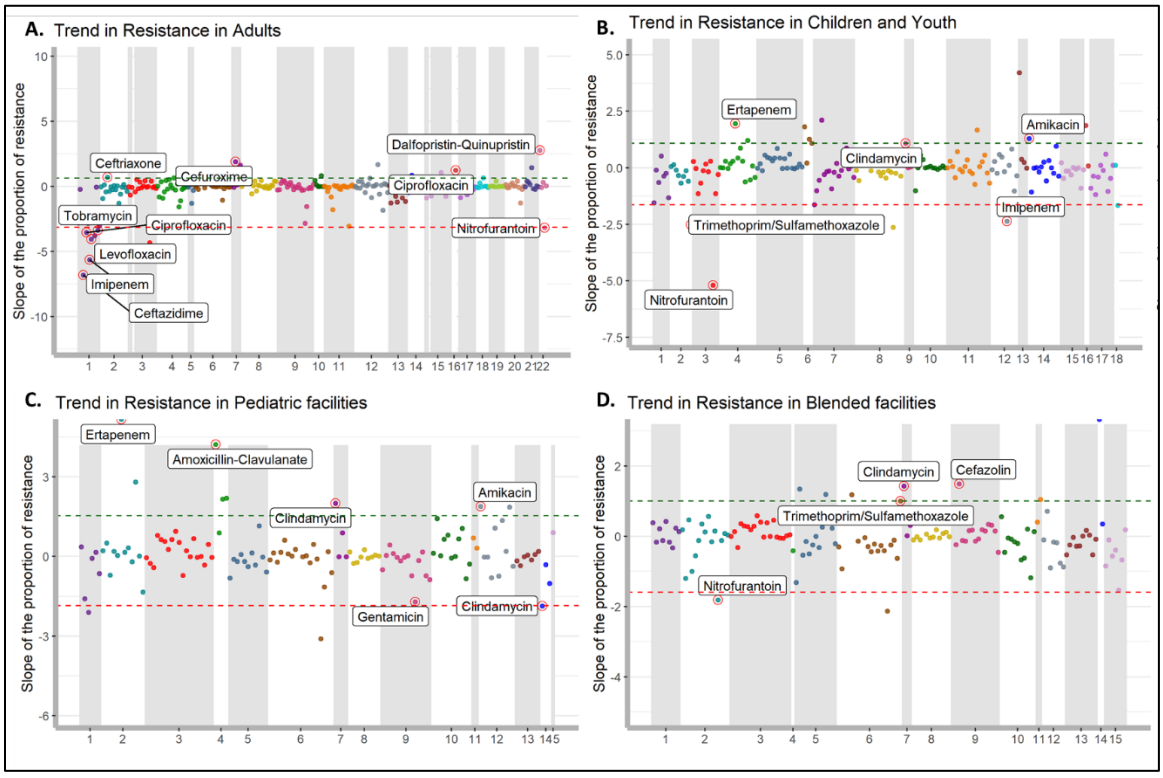

Figure 3.5. The pathogen-antibiotic combinations with a significant positive and negative trend for all the four groups

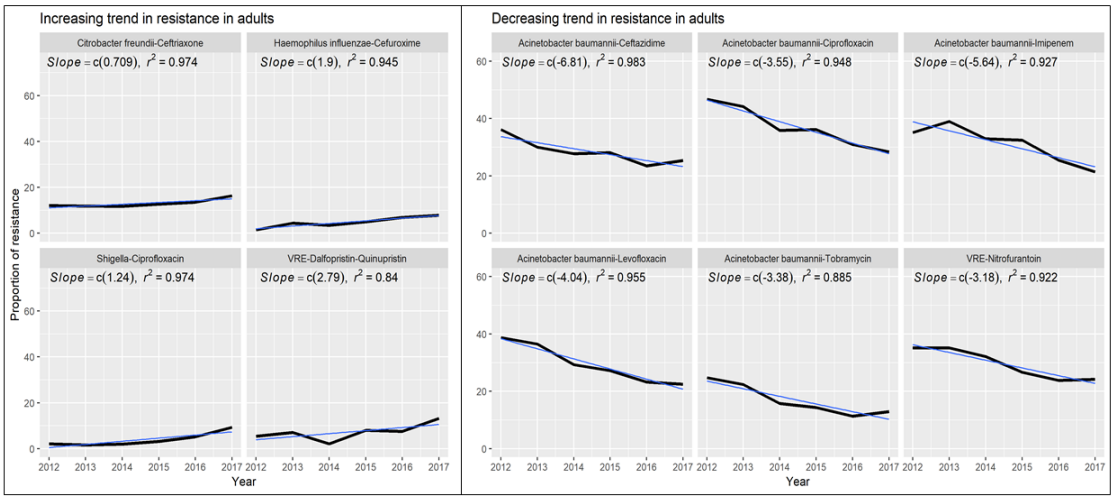

Figure 3.6. Patterns of increasing and decreasing trend in resistance of statistically significant pathogen-antibiotic isolates from adults.

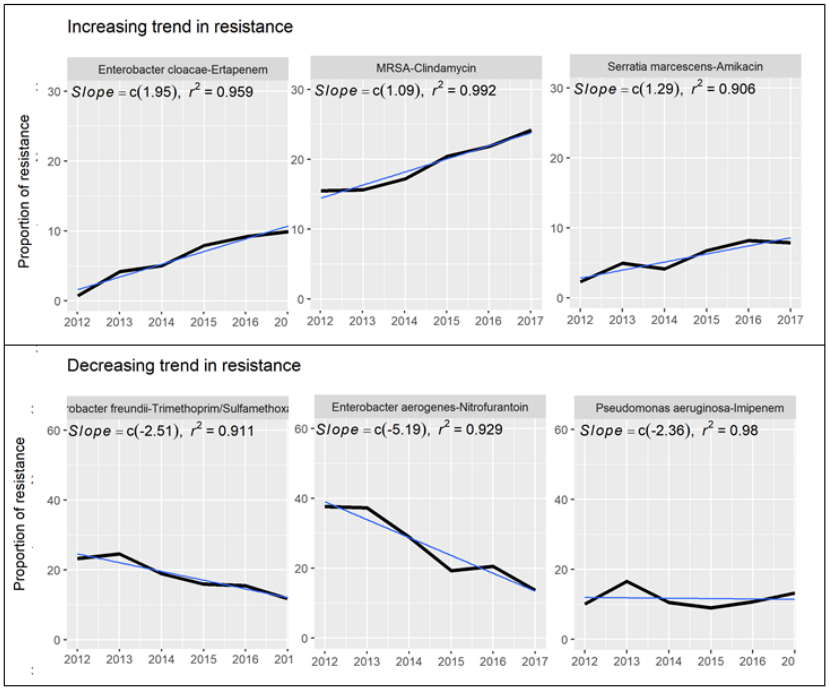

Figure 3.7. Patterns of increasing and decreasing trend in resistance of statistically significant pathogen-antibiotic isolates from children.

The C-MCS plot for adult vs children is shown in Figure 3.8A. Ertapenem resistant *E. cloacae* isolates from children increased significantly compared to adults (children: 0.7% to 9.8%; adults: 2.1% to 2.8%; p=0.00013). In contrast, ampicillin/sulbactam resistant *K. oxytoca* increased in adults but decreased in children (adults: 11% to 14%; children: 13% to 7%; R^2 =0.533) (Figure 3.8B).

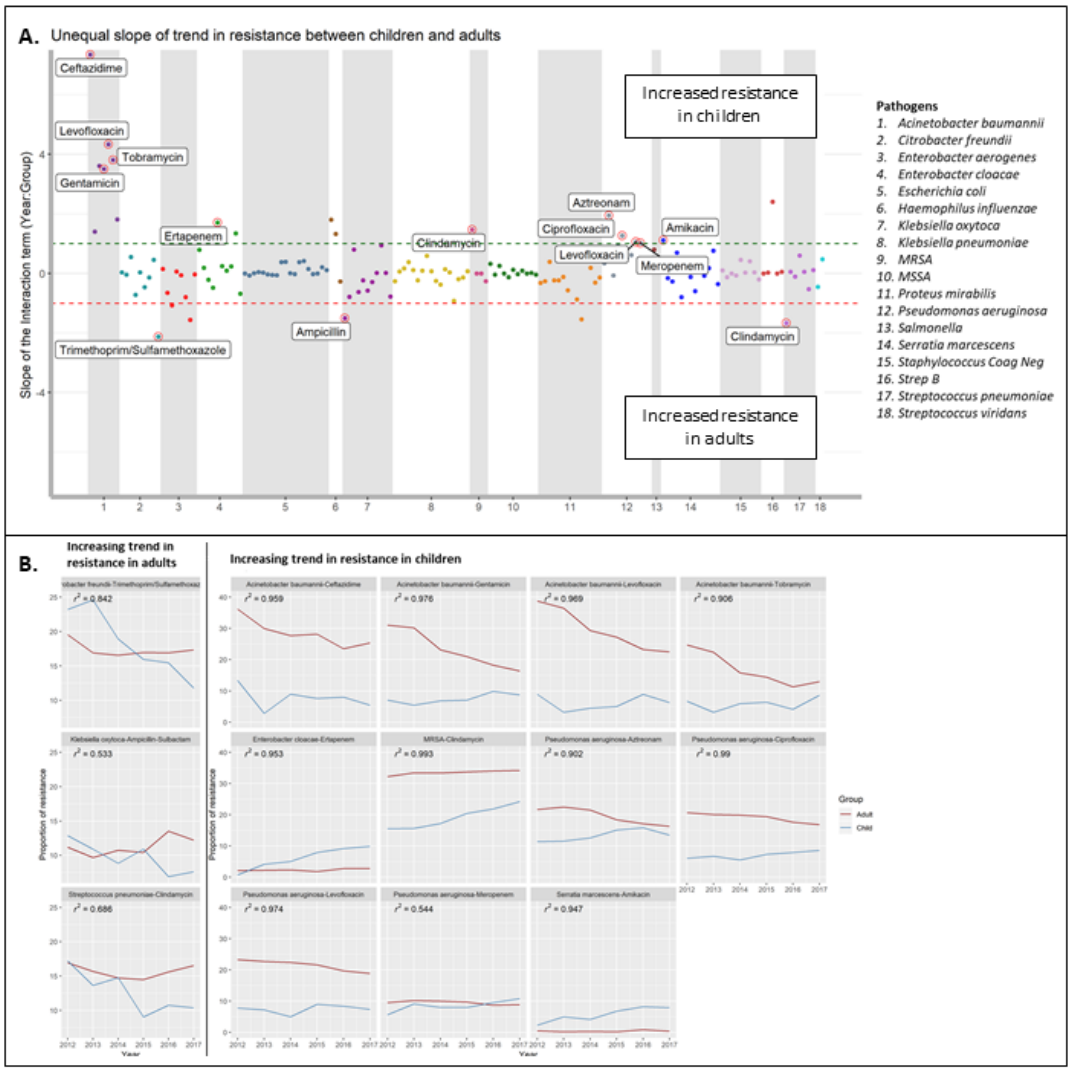

Figure 3.8. Adults Vs children. (A) C-MCS (Comparison Multiple Categorical Slope) plot (B) Higher increase in resistance among isolates from adults than children; Higher increase in resistance among isolates from children than adults

In pediatric facilities, ertapenem resistant *E. cloacae* increased from 0% to 27.1% (slope = 5.16, R^2=0.948, p=0.002) while gentamicin resistant *P. mirabilis* decreased from 8% to 0.8% (slope = -1.89, R^2=0.894, p=0.01) (Figure 3.9A). In blended facilities, cefazolin resistant *P. mirabilis* increased from 4% to 11% (slope = 1.5, R^2=0.85, p=0.02) while nitrofurantoin resistant *E. cloacae* decreased from 25% to 14% (slope = -1.81, R^2=0.71, p=0.03) (Figure 3.9B).

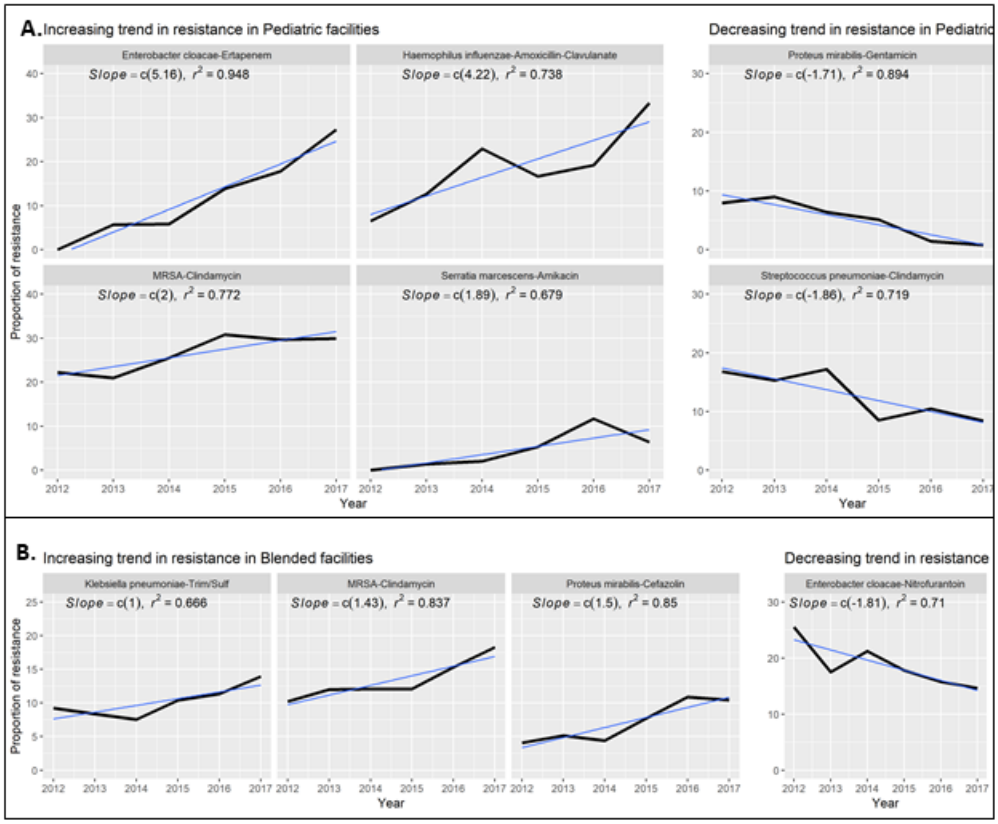

Figure 3.9. Patterns of trend in resistance among isolates from children by care-setting (A) Pediatric facilities (B) Blended facilities

The C-MCS plot for cultures from children in pediatric vs blended facilities is shown in Figure 3.10A. Imipenem resistant *P. aeruginosa* isolates from children

increased in pediatric facilities but decreased in blended facilities (Pediatric: 8% to 14%; Blended: 12% to 10%; R^2 =0.738). In contrast, ampicillin/sulbactam resistant *K. oxytoca* increased in blended facilities but decreased in pediatric facilities (Blended: 11% to 12%; Pediatric: 13% to 7%; R^2 =0.533) (Figure 3.10B).

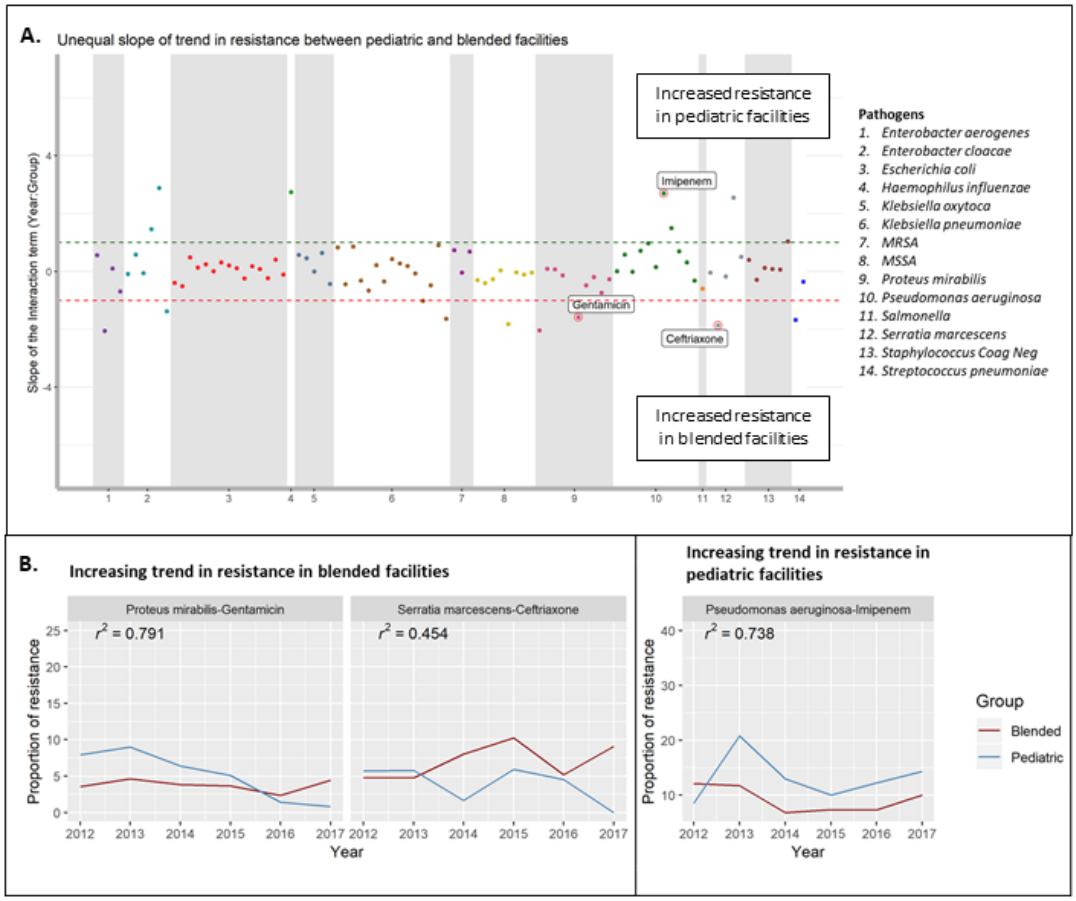

Figure 3.10. Pediatric facilities Vs blended facilities. (A) C-MCS (Comparison Multiple Categorical Slope) plot (B) Higher increase in resistance among isolates from children in blended than pediatric facilities; Higher increase in resistance among isolates from children in pediatric than blended facilities

3.4. Discussion

We evaluated variation in AR for 22 high priority pathogens based on age category of patient (child, adult), care setting for pediatric patients and over time. Several statistically significant changes in AR rates were observed between January 2012 and December 2017 as well as over time with respect to age and care-setting. Overall, we note a higher level of AR among isolates of the same pathogen for children compared to adults and children treated in pediatric facilities compared to those treated at blended facilities. However, we also note varying trends for individual bug-drug pairs.

Our findings with respect to the entire HF cohort indicated high resistance rates of gram-positive pathogens to clindamycin (Figure 3.2), consistent with a CDC report showing that clindamycin resistant Group B *Streptococcus* results in 31,000 infections and 1700 deaths per year (3). Our study also indicated high resistance rates of gram-negative (GN) bacteria to cephalosporins (ceftriaxone, cefuroxime, cefotetan and cefazolin). Emergence of cephalosporin resistant GN infections such as, ceftriaxone resistant *A. baumanii*, third-generation cephalosporin resistant *Klebsiella* and *E. coli* isolates can have a detrimental impact on clinical outcomes (158–161). The emerging trends in resistance rates to clinically relevant antibiotics are worrisome and may lead to the spread of life-threatening infections, especially for inpatient settings. Our study reports an increase in ciprofloxacin resistant *Shigella* spp., (Fig 4) which is consistent with a health advisory published by the CDC describing an increase in the number of reported cases of ciprofloxacin resistant Shigellosis (162).

Our study adds to the national concerns about AR as we show differences in resistance patterns between isolates from adults and children. At the baseline level, *A.*

baumanii were more resistant in isolates from adults when compared to children (Fig 3A). This was consistent with the literature indicating that carbapenem-resistant *A. baumannii* is increasing in adults. However, in isolates from children, there was a significant decrease in trend of resistance after 2008 which may be related to the expert guidance released by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology expert guidance in 2007 advising implementation of antimicrobial stewardship programs in acute care settings to combat MDR *A baumannii* during this time period (60, 163, 164). Another finding in our study indicates that *P. aeruginosa* isolates from children were more resistant than those from adults (Fig 3B). This was comparable to a recent analysis of over 87,000 *P. aeruginosa* isolates recovered from U.S. children that showed an increase in MDR *P. aeruginosa* from 15.4% to 26% between 1999–2012 (165). *P. aeruginosa* is known to be especially prevalent among children with cystic fibrosis (CF), up to 80%, but less common among adult CF patients (166, 167). An example of emerging trend among isolates from adults is cefuroxime resistant *H. influenzae* (Fig 5A). One possible explanation is the increased selective pressure due to the treatment guidelines for management of community acquired pneumonia in immunocompetent adults established by the American Thoracic Society and the Infectious Disease Society of America which recommends cefuroxime for influenza with bacterial superinfection (49).

We also evaluated variations in resistance patterns based on care setting. For example, we show that *K. pneumonia* had a higher baseline resistance in isolates from children treated in blended facilities (Fig 3C). *K. pneumonia* accounts for nearly 15% of all HAI (168). Therefore, it is possible that blended facilities could have a higher

proportion of *K. pneumonia* associated HAI than pediatric facilities. One key example based on both age and care-setting is the emerging trend of Ertapenem resistant *E. cloacae* isolates from children and especially within the pediatric facilities (Fig 5). Ertapenem-Resistant Enterobacteriaceae are identified as an important problem associated with an increased 30-day mortality and a significant variation in antibiotic treatment for children with infrequent use of combination therapy (169). This rising trend could be due to the emergence and spread of resistant clones which may be easily transmitted within health-care settings (45).

These patterns highlight the growing problem of bacteria developing resistance to first line therapies segmented by age and the type of care-setting. These trends are especially concerning for emergency department providers, because they are often the first point of contact for individuals presenting with these diseases and must make empiric antibiotic selections. Failure to identify and properly treat these organisms can have a devastating impact on patient outcomes (170). While institution specific antibiograms, exist, they are not universally available. One important strategy to combat AR is the use of care setting specific Antibiotic Stewardship Programs (ASPs) based on the type of facility and the age of the patient. ASPs work to promote the appropriate use of antibiotics and to decrease the spread of resistant organisms (147). ASPs have optimized antibiotic use and reduced healthcare costs but their effectiveness will be limited until they become more specific to the type of population and care setting (171, 172). Our work suggests strategies to offer ASPs informed by national and local data.

Our study also identified patterns with negative trends in resistance, including drops in *A. baumanii* resistance in the HF cohort and among adults. The 2019 CDC report

on *A. baumanii* indicated that resistance to fluroquniolones, extended-spectrum β-lactam, ampicillin/sulbactam and trimethoprim/ sulfamethoxazole has been decreasing between 2013 – 2017, consistent with the findings of this study (3). The increased use of carbapenems as an empirical treatment for *A. baumannii* infections has potentially reduced the selective pressure to develop resistance to other antibiotics. These negative trends highlight that successful ASP decrease AR bacteria over time.

Our study has known limitations. First, it could not be ascertained whether the infections were community acquired or nosocomial or whether resistance was primary or secondary, the AR rates were generalized to the full study population. Second, despite controlling for the total number of encounters, confounding variables for severity of resistance may exist. However, this does not change our result with respect to the proportion of baseline resistance or trend in resistance. Third, our work is observational and does not provide insights into the drivers for the changes in AR patterns.

Our study also had several strengths. First, we created the MCS and C-MCS plots, a novel methodology plotting the slope of the proportion of resistance segregated by pathogen-antibiotic combinations to identify significant increase/decrease in the trend in resistance and enabling easy comparison between groups. We were able to discern patterns, identify linear relationships in 302 pathogen-antibiotic pairs, repeat the analysis for four groups and focus on significant insights readily apparent in the MCS and C-MCS plots. Second, we used a national data set that combines patient and facility level characteristics and validated the accuracy of the HF data source for the first time with internal antibiogram data. Third, we compared the level of resistance and the trend in AR at the care-setting level for the first time.

This study described prevalence and trends of AR among common gram-positive and gram-negative pathogens factoring the age of the patient and the care setting. Our methods can influence the development of data-driven ASP at local, regional and national levels.

CHAPTER 4

DIFFERENCES IN THE PREVALENCE OF DEFINITIVE BUG-DRUG MISMATCH (BDM) THERAPY BETWEEN ADULTS AND CHILDREN BY CARE-SETTING

4.1. Introduction

Inappropriate antibiotic use poses a major challenge to public health in terms of increasing antibiotic resistance (AR), the likelihood of preventable adverse drug events (ADE), and the use and cost of health care services (173–175). The Centers of Disease Control (CDC) in the US reported that 55.7% of patients from 323 hospital settings were given antibiotics during their hospital stay (176). Within the outpatient setting in the US, there were an estimated 249.8 million total antibiotic prescriptions, equivalent to 763 prescriptions per 1000 persons in the year 2018 (177). CDC estimates that total inappropriate antibiotic orders may approach 50% of all outpatient antibiotic use (178, 179). An important and modifiable category of inappropriate antibiotic therapy include Bug-Drug Mismatch (BDM) occurrence in which the antibiotic therapy is given after the antibiotic susceptibility test result of the isolated pathogen was verified to be resistant (24, 25, 43). BDM is preventable with timely access to AST results and is an important quality concern as they hinder the opportunity to target susceptible antibiotics to known pathogen or to optimize empiric treatment.

Antibiotic use varies significantly between children and adults (17, 18). Among pediatric patients, antibiotics are the most commonly prescribed drug class, and more

than half of hospitalized United States (US) children receive antibiotics (180). Around 70,000 children visited the ED for antibiotic-related ADEs from oral antibiotics each year between 2011 to 2015 twice as often as adults. Many of these visits (41%) were from children 2 years or younger (181). Additionally, substantial differences exist between stand-alone pediatric sites and blended facilities caring for children and adults, including patient characteristics, clinical training, patient outcomes and distinction in guideline-concordant antibiotic use for children (12–14, 182). Pediatric facilities vary substantially in their use of antibiotics among children. Children admitted to non-pediatric emergency departments were more likely to receive inappropriate antibiotics (15).

To date, evaluation of appropriate pediatric antibiotic prescribing in US populations has been most extensive in outpatient settings (183, 184). While multiple studies in adult inpatient populations have demonstrated that 30%–50% of antibiotics are prescribed inappropriately, few studies have focused on US pediatric populations, and these reflect only single centers or specific diagnoses or interventions (19–22). Furthermore, most studies do not include detailed assessments of prescribing appropriateness. And there are no studies that provide estimates on the prevalence of BDM in pediatric populations between pediatric facilities and blended facilities. National estimates indicate that only 10% of pediatric hospitalizations occur in a pediatric children's hospital, which suggests that research on antibiotic use in other facility types is also needed to inform pediatric antimicrobial stewardship efforts (185).

Data derived from EHRs loaded into multi-institutional data warehouses provide a powerful resource for examining these issues. One such data resource, Cerner Health Facts™ (HF), includes granular micro-susceptibility test results and inpatient medication

orders from multiple sites (151). The primary objective of this study is to evaluate the overall BDM prevalence using the unique combination of laboratory and medication EHR data. The secondary objective is to compare the prevalence of BDM between children and adults as well as among children treated in primarily pediatric facilities and blended facilities.

4.2.Methods

4.2.1. Data Source

We derived the study data from Cerner Health Facts database (Kansas City, MO, USA) populated by the daily extraction of discrete EHR data from participating organizations. HF data is de-identified in a manner compliant with US Health Insurance Portability and Accountability Act (HIPAA) standards. In the 2018 version of HF, which includes 54 million inpatient medication orders, 29 million microbiology results and 5 million micro susceptibility results from 21 million patients in 473 facilities. The Children's Mercy Institutional Review Board has designated research with HF data as "non-human subjects research."

4.2.2. Data Definition

The efficacy of the antibiotics against the pathogens is interpreted as susceptible (S) if the isolates are not inhibited by the recommended dosage of antibiotic and there is a bacterial growth in the presence of the antibiotic; and resistant (R) if the isolates are inhibited by the recommended dosage of antibiotic (152). An antibiotic order is identified as BDM if the isolated pathogen is resistant to the antibiotic and the antibiotic is ordered

within 3 weeks after the antibiotic susceptibility test (AST) result was verified; and appropriate if the isolated pathogen is susceptible to the antibiotic.

4.2.3. Study Design

We conducted a retrospective study of patients with microbiology result, AST results and antibiotic orders within the same visit between 2009-2017. We included 14 clinically relevant pathogen groups: *Acinetobacter, Citrobacter, Enterobacter, Enterococcus, Escherichia, Hemophilus, Klebsiella,* MRSA, MSSA*, Proteus, Pseudomonas, Salmonella, Serratia, Streptococcus* (186). In order to exclude positive cultures that were possibly due to contamination, pathogens were further filtered on sterile source sites (abdomen, abscess, blood, body fluid, bone, and incision). We included AST results of the pathogens which reported valid susceptible, intermediate, or resistant results with a valid date stamp. Critically important FDA recommended antibiotics were included in the study (187); topical, ophthalmic, or OTIC antibiotics were excluded. Every antibiotic order had an associated valid AST result within the same encounter. We separated the HF study cohort into four groups: encounters of the isolates from children (Age <18) (Group I); and adults (Age >18) (Group II); isolates of children from pediatric facilities (Group III) and isolates of children from blended facilities (Group IV). Facilities where the mean age of patients is less than eighteen were identified as likely pediatric facilities and facilities treating both adults and children were identified as blended facilities (Figure 4.1).

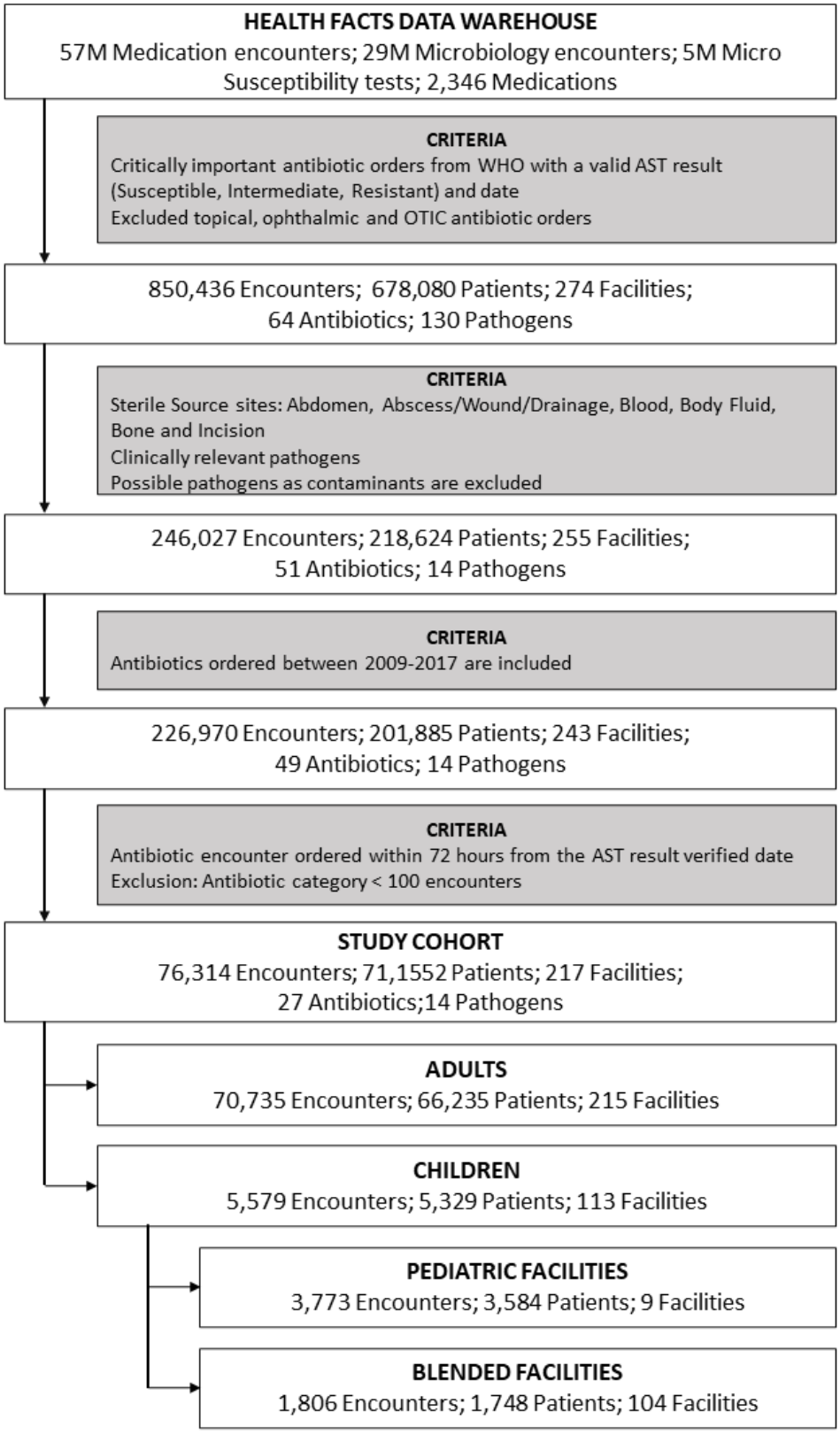

Figure 4.1. Data extraction and study design

4.2.4. Analysis

The unit of analysis is an antibiotic order per encounter. We examined the prevalence of BDM for important antibiotics and across relevant pathogens. The prevalence of BDM is calculated as the number of BDM antibiotic orders by the total number of antibiotic orders. We compared the BDM prevalence between children and adults as well as between pediatric and blended facilities using Fisher's exact test or the Pearson Chi-square test. All p-values were two-sided. R version 3.3.1 was used for all data management and analysis.

4.3.Results

4.3.1. Data Characteristics

We included antibiotic orders and AST results of 14 pathogen groups (*Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Enterococcus* spp., *Escherichia* spp., *Haemophilus* spp., *Klebsiella* spp., MRSA, *Proteus* spp., *Pseudomonas* spp., *Salmonella* spp., *Serratia* spp., *Staphylococcus* spp., *Streptococcus* spp.) screened across 27 antibiotics (amikacin, amoxicillin/clav, ampicillin/sulbactam, ampicillin, aztreonam, cefazolin, cefepime, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, ciprofloxacin, clindamycin, doxycycline, ertapenem, erythromycin, gentamicin, levofloxacin, linezolid, meropenem, moxifloxacin, oxacillin, pip/tazo, rifampin, tigecycline, tobramycin, vancomycin). Vancomycin was the most ordered antibiotic at 24% (18,262 encounters) followed by levofloxacin at 15% (11,284 encounters). Isolate samples were recorded from 6 distinct body source sites. Abscess and blood isolated pathogens constituted 81%

of all isolates. The majority of the susceptibility tests used minimal inhibitory concentration (MIC) or Kirby- Bauer (KB) method.

The total study cohort consists of 76,314 encounters from 71,552 patients in 217 facilities from 64 non-affiliated organizations. Most facilities (72%) were non-teaching institutions, and the majority were urban (83%). More than half of the facilities had between 200-500 beds (53%), 41% had fewer than 200 beds and 6% had more than 500 beds. Group I consists of 66,235 adults (93% of the HF study cohort) from 215 facilities while Group II consists of 5,329 children (7% of HF study cohort) from 113 facilities. Group III consists of 9 pediatric facilities treating 3,584 children. Group IV consists of 104 blended facilities treating 1,748 children (Figure 4.1).

4.3.2. BDM Prevalence

The BDM prevalence in the overall study cohort was 7% (5,418 encounters). Erythromycin was the antibiotic with the highest BDM prevalence at 52% (133 encounters) for all bacterial infections. This was followed by cefazolin at 17% (5631 encounters) and ampicillin/sulbactam at 13% (1,295 encounters) (Figure 4.2).

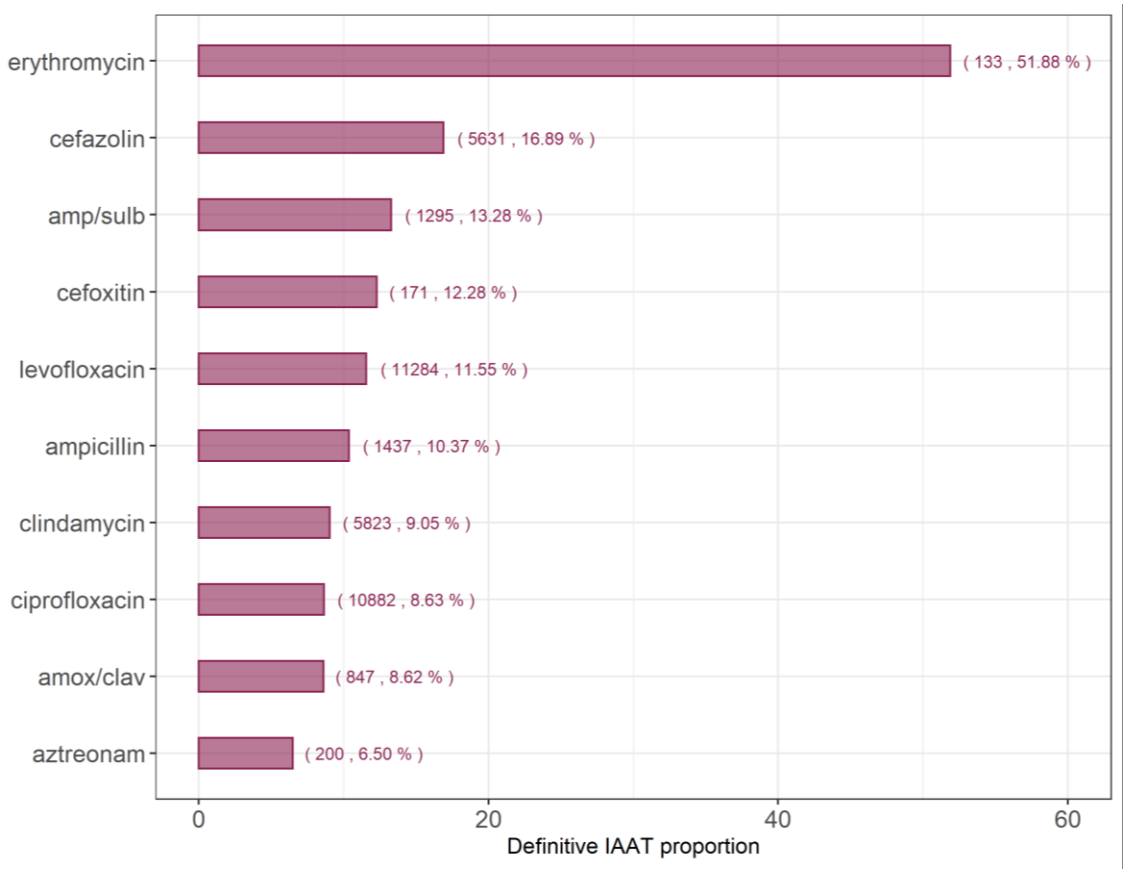

Figure 4.2. Top 10 antibiotics with the highest BDM prevalence. (No. of BDM encounters, BDM Prevalence %)

At the pathogen-antibiotic level, erythromycin ordered for *Enterococcus* sp., infections had the highest BDM prevalence of 58%, cefazolin ordered for *Citrobacter* sp., infections at 51% and ampicillin/sulbactam ordered for *Citrobacter* sp., infections at 21% (Figure 4.3).

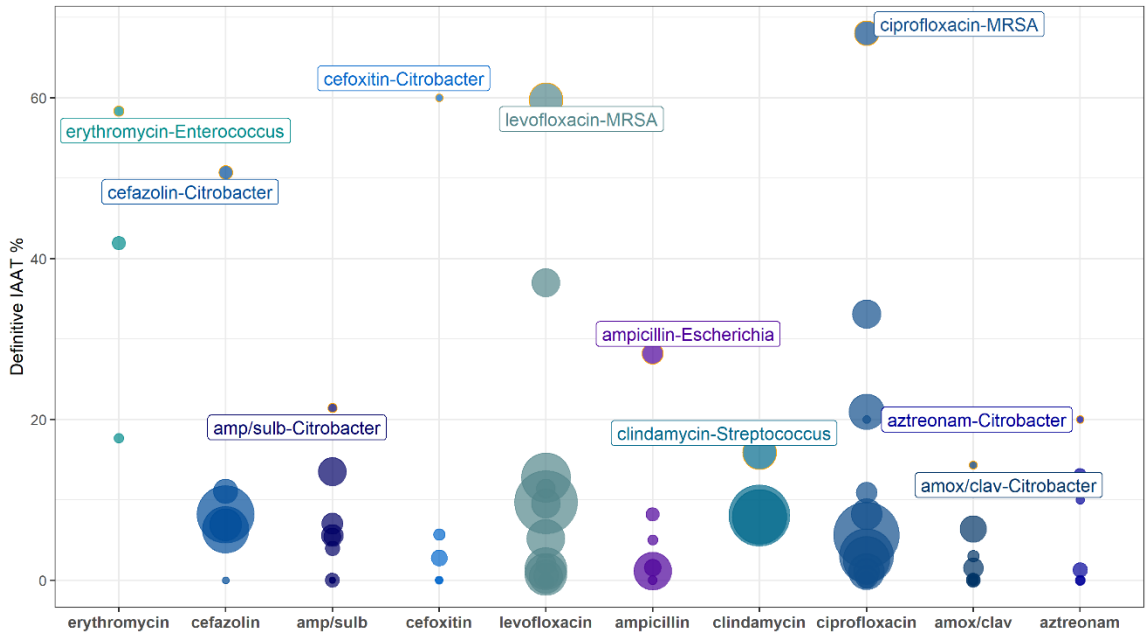

Figure 4.3. Top 10 antibiotics with the highest BDM prevalence by bacterial infections. Highest BDM prevalence by pathogen for every antibiotic are highlighted and labelled. Size of the circle corresponds to the number of encounters for every pathogen-antibiotic combination.

The overall difference in the prevalence of BDM was higher in adults when compared to children (7% Vs 5%). We compared BDM prevalence patterns at the antibiotic level based on age group (Figure 4.4A, 4.4B) and care setting (Figure 4.4C, 4.4D). For example, ampicillin/sulbactam ordered for adults had a higher BDM prevalence than children (16% Vs 7%, $p<0.0001$). Other BDM associations were more common for children, for example cefazolin ordered for children had a higher BDM prevalence than adults (23% vs 18%, $p<0.0001$). Additionally, cefazolin ordered for children in blended facilities had a higher BDM prevalence than children in pediatric facilities (27% vs 21%, $p<0.0001$). Few BDM associations were slightly more common among children in pediatric facilities than blended facilities, such as the BDM prevalence for meropenem (6% vs 2%).

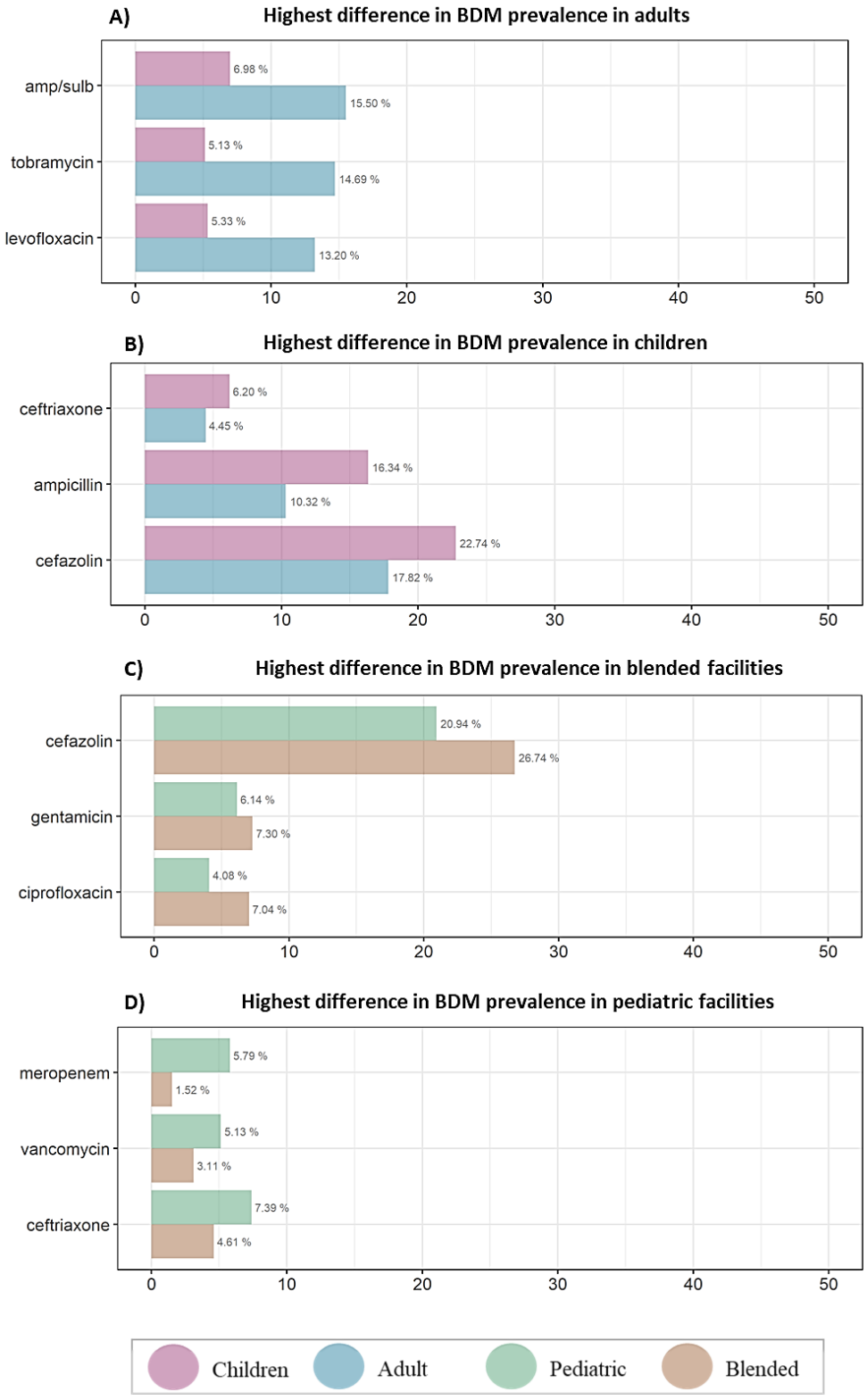

Figure 4.4. Top three antibiotics with the highest difference in BDM prevalence between subgroups.

We compared BDM prevalence patterns at the bug-drug level based on age group (Figure 4.5A, 4.5B) and care setting (Figure 4.5C, 4.5D). For example, gentamicin ordered for gentamicin resistant *Serratia* and MRSA isolates from adults had a higher BDM prevalence than children (14% Vs 3%, $p<0.0001$; 16% Vs 0%, $p<0.0001$). Several BDM associations at the bug-drug level were more common in children than adults, such as cefazolin ordered for cefazolin resistant *Staphylococcus* isolates (24% vs 12%, $p<0.0001$). More specifically, cefazolin ordered for cefazolin resistant *Staphylococcus* isolates from children in pediatric facilities had a higher BDM prevalence when compared to children in blended facilities (16% vs 10%, $p <0.0001$). Other bug-drug combinations had a slightly higher BDM prevalence among children in blended facilities than pediatric facilities, such as gentamicin ordered for gentamicin resistant *Escherichia* isolates (10% vs 7%, $p<0.01$).

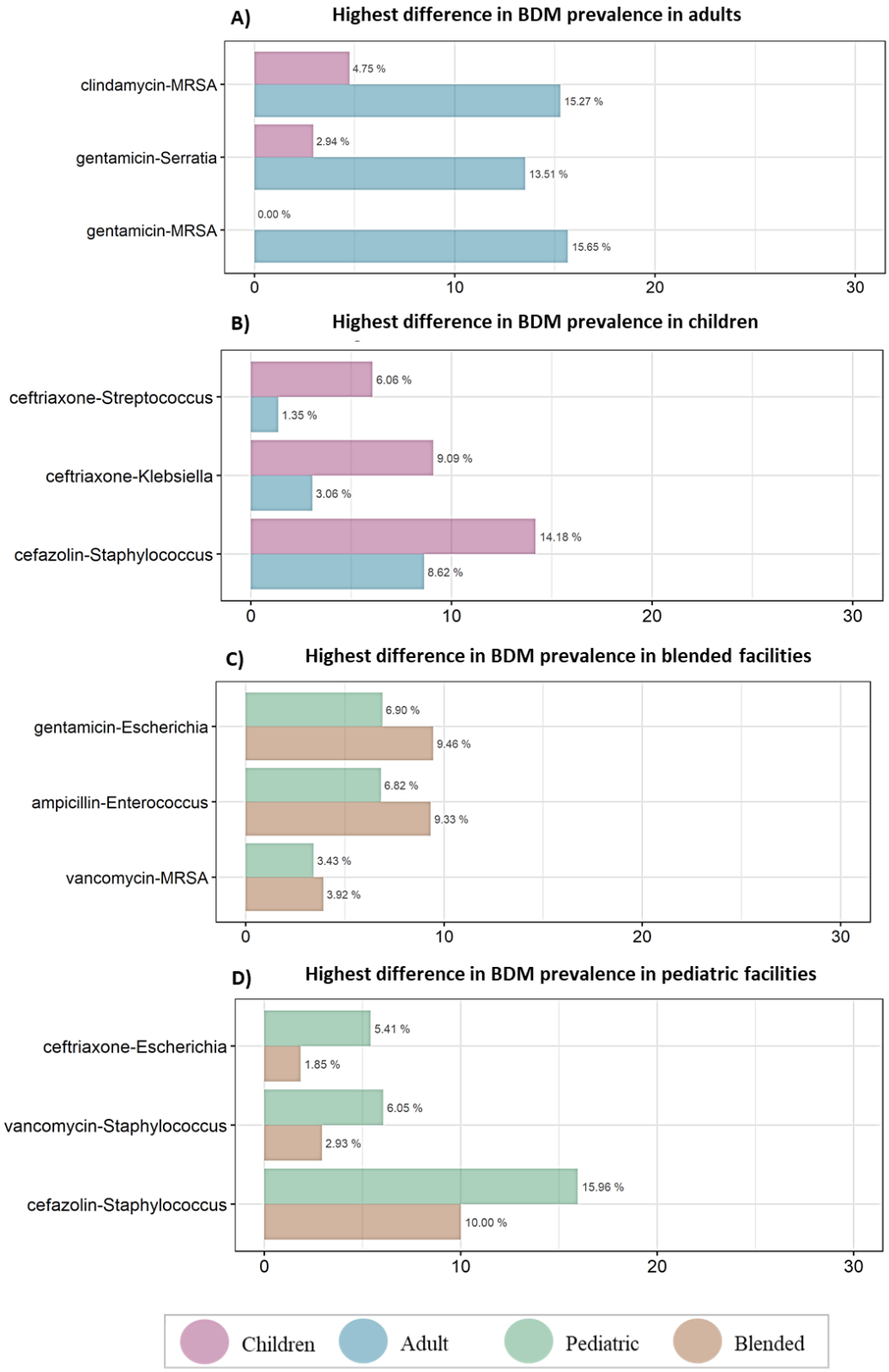

Figure 4.5. Top three pathogen-antibiotic pairs with the highest difference in BDM prevalence between subgroups.

4.4.Discussion

We use "real world" de-identified EHR data to evaluate the prevalence of bug-drug mismatch (BDM) between laboratory results and medication orders. Using this approach, we found that the BDM prevalence for several critically important antibiotics differed between children and adults as well as within pediatric and blended facilities.

Our study indicated that adults when compared to children had a higher BDM prevalence especially for ampicillin/sulbactam, tobramycin and levofloxacin. The higher BDM prevalence in adults probably relates to the increasing resistance of pathogens to ampicillin/sulbactam and levofloxacin in adults (188, 189); cautious use of aminoglycosides (tobramycin) in children due to variability in the dosing regimen and pharmacokinetics (190, 191). Since tobramycin exhibits the toxic effects common to aminoglycosides, i.e., ototoxicity and nephrotoxicity, interventions to decrease BDM prevalence among adults to maximize therapeutic outcomes and minimize adverse consequences are important (192).

At the baseline level, 5% of the children in pediatric and blended facilities had a BDM in our study. These results are in agreement with a multi-center study involved examining the medical records of 11,784 children who had been prescribed antibiotics in 32 U.S. pediatric hospitals found 6% of the children received at least one suboptimal antibiotic due to BDM (193). Our study shows specific bug-drug combinations with particularly high mis-match rates. For example, cefazolin ordered for *Staphylococcus* infections had a higher BDM prevalence among children than adults, particularly among children in pediatric facilities. Cefazolin treatment may be associated with clinical failure for serious MSSA infections due to the inoculum effect of cefazolin (194, 195). The

higher BDM prevalence could be related to the significant increase in cefazolin usage in pediatric facilities (19). These findings also parallel a recent study that showed continued inappropriate administration of prophylactic antibiotics before surgery among children in pediatric facilities of which cefazolin was most frequently prescribed (196). .

Overall, erythromycin had higher BDM prevalence compared to any other antibiotic. Even though our findings agree with a single center study on inappropriate antibiotic orders in soft tissue infections (197), some or most of erythromycin prescriptions could have been ordered as a prokinetic agent which results in increased GI motility (198). The use of erythromycin as a prokinetic agent still does not constitute prudent antimicrobial prescribing and should be avoided as it can increase the emergence and spread of antibiotic resistance and the likelihood of *Clostridium difficile* disease (199).

In this study, we did not analyze antibiotic use for empiric therapy, which is ordered for a patient with symptoms and signs of a serious infection before identification of the bacteria and before susceptibility test results are available (200). It is essential that empiric and definitive antibiotic therapy be separately defined, because interventions aimed at increasing the proportion of patients who receive appropriate empiric and definitive therapy would be inherently different. In populations in which inappropriate empiric therapy is associated with increased mortality mitigations such as clinical guidelines, hospital antibiograms, and consultations with infectious diseases specialists may improve the likelihood that empiric therapy is appropriate. In contrast, interventions aimed at increasing appropriate definitive therapy would involve facilitation of prompt access to the final culture and susceptibility test reports, as well as full comprehension of

the implications for treatment. Bug-drug mismatches as reported in this study are easily preventable with timely access to AST results.

One proposed method of attenuating the rise of resistance is reducing unnecessary antibiotic use such as BDM through antimicrobial stewardship programs (ASPs) (24). Electronic health records (EHR) and clinical decision support systems (CDSS), provide real-time alerts updated when new microbial culture results become available or antimicrobial changes occur. These systems help ASPs by providing a means to track resistant pathogens, antimicrobial utilization, data on patient-specific microbiology cultures and susceptibilities, patient comorbidities, adverse drug reactions, and drug-drug interactions (201) . CDSS have both prebuilt and customizable ASP–related alerts which can be created for specific patient care units or for an entire institution (202). Prior studies assessing the impact of CDSS on ASPs have demonstrated process and economic benefits of these technologies by reducing the use of broad-spectrum antibiotics, improving antibiotic dosing, increased number of interventions and optimizing the selection of antibiotics (203–205). However, additional research is required to determine the true impact of CDSS on ASP and the goal of improved patient outcomes through optimized antimicrobial use. Another study evaluated the utility of the CDSS tool which provided a BDM alert where 64% of the blood culture isolates and 56% of the wound culture isolates required intervention (25). A case study on the ASP team in a community hospital in Illinois reported the use of the CDSS to create multiple algorithms to automatically identify BDM and streamlined antibiotic therapy for patients (206). The majority of these studies on ASP have been conducted in adult facilities. The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

recommends further research in pediatric settings (109). Few studies on ASP implementation in pediatric and blended facilities have demonstrated decrease in antibiotic misuse (207, 208).

Our work is based on a large, multicenter cohort and has several strengths. First, our data has representation of different regions in the US and a large sample size, which reduces biases of local origin, increases external validity and provides statistical power. Second, this is the first comprehensive exploration study comparing the BDM prevalence within age groups and care-setting.

However, our study also had known limitations. First, because this study was retrospective, there is no way to determine whether the choice of antibiotics for the study population were confounded by factors beyond our recognition in the de-identified data. Second, we did not evaluate the impact of the BDM on antibiotic adverse events or other clinical outcomes in this work. Our study is observational in nature, which prevents us from determining causal relationships.

In conclusion, we describe the first use of large scale EHR data to evaluate BDM at 217 US healthcare facilities from 64 non-affiliated organizations. We identify the importance of factoring the age of the patient and the care setting to address the prevalence of BDM. Our findings clearly demonstrate an opportunity for further outcomes research and for readily implemented interventions such as development of data-driven CDSS tools to assist ASP at local, regional and national levels.

CHAPTER 5

PREDICTING BUG-DRUG MISMATCH (BDM) OCCURRENCE IN EHR DATA USING MACHINE LEARNING MODELS

5.1. Introduction

Inappropriate antibiotic therapy is an important driver for the global increase in antibiotic resistance (AR) (72, 76). The CDC estimates that more than 70% of the bacteria responsible the 2 million infections acquired in US hospitals each year are resistant to at least one commonly used antibiotic, and 20% to 50% of antibiotics prescribed in US acute-care hospitals are unnecessary or inappropriate (209). In addition to increase in AR, consequences of inappropriate antibiotic therapy also include increase in disease severity, disease length, health complications, risk of death, healthcare costs and re-hospitalization (23, 91–94).

An important and modifiable category of inappropriate antibiotic therapy is Bug-Drug Mismatch (BDM) occurrence in which the antibiotic therapy is given after the antibiotic susceptibility test result of the isolated pathogen was verified to be resistant. Patients with a BDM occurrence have questionable therapeutic benefit and increasing adverse outcomes as the patient is prescribed incorrect antibiotic to which the pathogen is resistant (23). However, little information exists on the identification of independent risk factors for BDM occurrence which may be useful for the development of preventive measures like development of Clinical Decision Support (CDS) tools as part of Antibiotic

Stewardship Programs (ASP) (24, 25). Data derived from Electronic Health Records (EHR) loaded into multi-institutional data warehouses containing facility metrics, clinical conditions of the patients, antibiotic orders and microbiology results provide a powerful resource for addressing these issues.

Clinical EHR systems and their rich, heterogeneous data provide opportunities for impactful secondary use (210). Fully taking advantage of such large repositories of data is a challenge because of sheer complexity of the data (151). Machine learning (ML) methods offer nonlinear and nonparametric methods to address such challenges by their ability to accommodate larger feature sets, to identify implicit or explicit feature interactions and identify subtle patterns in data while remaining robust to problems in data quality and completeness (211). While most of the published IAAT prediction studies have focused on logistic regression models, ML models have potential in solving complex and challenging clinical outcome problems (26–31). ML procedures are capable of processing complex nonlinear relationships between predictors, yield more stable predictions and high-order effects in the predictive variables, which are difficult to handle with conventional parametric logistic regression methods (212, 213). Although there are ML studies predicting antibiotic resistance (32–34), there are no ML studies on predicting antibiotic use combined with AR.

Therefore, the first goal of this study was to identify the likely risk factors associated with BDM occurrence using logistic regression. The second aim was to develop machine learning models that predict the occurrence of BDM and compare their predictive performance with the reference logistic regression model.

5.2. Methods

5.2.1. Data Source

We derived the study data from Cerner Health Facts database (Kansas City, MO, USA) populated by the daily extraction of discrete EHR data from participating organizations. HF data is de-identified in a manner compliant with US Health Insurance Portability and Accountability Act (HIPAA) standards. This work was performed with the 2018 version of the Health Facts which includes data from 664 facilities associated with 100 non-affiliated health systems. This version of the HF data includes 69 million patients, 507 million encounters, 29 million microbiology results, 729 million medication orders, 989 million diagnoses and 6.9 billion clinical events. The Children's Mercy Institutional Review Board has designated research with HF data as "non-human subjects research."

5.2.2. Study Design

We conducted a prognostic study of combined data of patients with a microbiology culture result, antibiotic susceptibility test (AST) results and antibiotic orders within the same visit between 2009-2017. We included clinically relevant pathogens (133), critically important antibiotics from WHO (187), samples obtained only from sterile source sites to exclude pathogens as possible contaminants. We excluded encounters that did not have valid AST test result or interpretation. We excluded antibiotic orders which were topical, ophthalmic, or OTIC.

5.2.3. Study Variables

Every antibiotic order was either classified as a BDM if the isolated pathogen was resistant to the antibiotic and the antibiotic was ordered within 3 weeks after the AST result was verified; or appropriate if the isolated pathogen was susceptible to the antibiotic. We included patient demographic characteristics such as age group, sex, race; and facility characteristics such as census region, urban/rural status, teaching facility status, bed size, acute status, freestanding pediatric facility status. There were 27 critically important antibiotics and if a patient was prescribed to more than one antibiotic, we defined it as combination therapy. There were 14 clinically relevant pathogens and if a patient had more than one isolated pathogen we defined it as polymicrobial bacteremia. Turn-around-time for the AST test was defined as the time difference between the ordered date and result verified date). A patient was classified as expired based on the discharge disposition (expired or expired at home, expired in a medical facility or expired place unknown). We also included source site of the culture sample; year of the encounter; duration of the hospital stay; antibiotic therapy duration; presence of surgery and admission to ICU. The most common patient comorbidities associated with inappropriate antibiotic therapy were included: Sepsis, cardiovascular disease, diabetes, cancer, hypertension, neurological disorder, hypothyroidism, psychological disorder, anemia, renal failure, liver disease, rheumatoid arthritis and fluid electrolyte disorder (92, 94, 214, 215). The severity of comorbidities were calculated by the Elixhauser Van Walraven weighted score in which a higher score indicates greater severity (216).

5.2.4. Analysis

We conducted multiple imputation using the random forest method for variables with missing data: teaching status of the facility (missing values: 6.2%), mortality (12%), antibiotic therapy duration (7.8%), admission to ICU (8%). Random forest imputation is a nonparametric algorithm that can accommodate nonlinearities and interactions and does not require a particular parametric model to be specified (217). Missingness was imputed using all the variables in the study cohort.

Descriptive statistics were implemented to summarize the patients' characteristics as mean (SD) or proportions. Chi-square or Fisher's exact test for the categorical data and Student's -test or Mann-Whitney test for the continuous data were employed to compare data between different groups.

To predict the probability of BDM occurrence, we developed the reference model (logistic regression model) and 4 machine learning models in the training set (70% random sample). Using the predictors stated above, we constructed 4 machine learning prediction models: (i) logistic regression with lasso regularization (218), (ii) random forest (219), (iii) gradient-boosted decision tree (220), and (iv) deep neural network (221). Lasso regularization extends standard regression models by enabling us to select important predictors (feature selection), more interpretable and clinically useful when compared to a standard logistic regression model using many predictors. For the lasso regression, we chose the regularization parameter (lambda). This gives the minimal misclassification error rate in order to penalize large coefficients from small sample sizes. This penalty function (minimal lambda) shrinks large coefficients toward 0, minimizing

potential overfitting (222). The minimal lambda was calculated using 10-fold cross-validation using the glmnet package (218).

Random forest is an ensemble of decision trees created by using bootstrap samples of the training data and random feature selection in tree induction. In this model, we used out-of-bag (left-out samples after bagging) estimation to measure the prediction errors (223).

Gradient-boosted decision tree is another ensemble approach—an additive model of decision trees estimated by gradient descent. For the random forest and gradient-boosted tree models, we used a grid search strategy to identify the best combination of hyperparameters by using the ranger and caret packages (219, 220). In the lasso regression and gradient-boosted tree models, we used 10-fold cross-validation to measure the prediction error with a smaller variance than that from a single train-test set split (224).

Deep neural networks are a class of machine learning algorithms consisting of multiple layers of nonlinear processing units to learn the value of the parameters that result in the best prediction of outcome. In the deep neural network, we constructed 5-layer feedforward model with adaptive moment estimation optimizer using Keras implemented in R statistical software (225). For the deep neural network, we developed the final models by manually tuning the hyperparameters, such as the number of layers and hidden units, learning rate, learning rate decay, dropout rate, batch size, and epochs, using the keras package (Figure 5.1)(221). In this model, to minimize potential overfitting, we used dropout that randomly removes portions of units in the network,

ridge regularization that shrinks large coefficients, and batch normalization that normalizes the means and variances of layer inputs (226, 227).

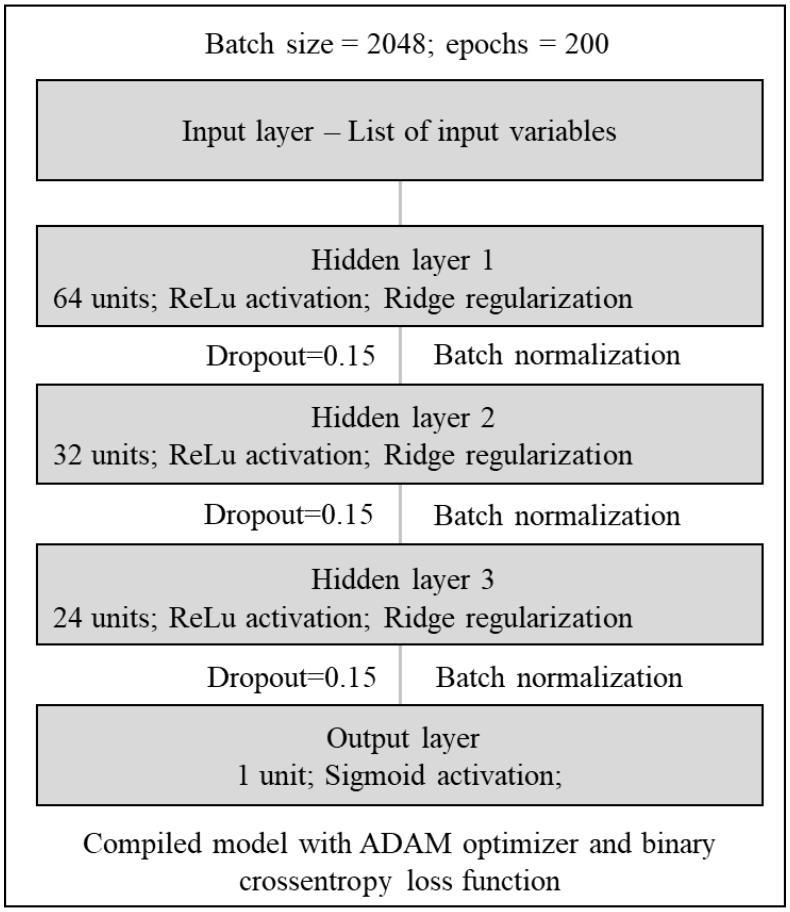

Figure 5.1. Hyperparameters for deep neural network model

In the test set (30% random sample), we measured the prediction performance of each model by computing (1) accuracy (percentage of correct predictions) (2) C-statistics (ie, the area under the receiver operating characteristic [ROC] curve), (3) prospective prediction results (ie, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio).

To gain insights into the contribution of each predictor to machine learning models, we also computed the variable importance in the gradient-boosted decision tree and random forest models for each outcome. The variable importance is a scaled measure to have a maximum value of 100. A DeLong test was used to compare ROC curves (228). We considered 2-sided $P < .05$ to be statistically significant. All analyses were performed with R statistical software version 3.4.1 (R Foundation for Statistical Computing).

5.3. Results

5.3.1. Characteristics of Study Cohort

The study cohort consists of 72,538 encounters from 767,971 patients in 215 facilities. The majority of the patients were between 18-65 years old (50%), and 52.6% were male patients. Most encounters were from teaching institutions (71%), and the majority were in urban environments (83%). More than half of the encounters were from facilities between 200-500 beds (65%), 25% had more than 500 beds and 7% had less than 100.

The most commonly identified antibiotic therapy were combination therapy (18%) followed by levofloxacin (11%). The most commonly identified pathogens were MSSA (21.2%) followed by *Escherichia* (21%). Abscess and blood isolated pathogens constituted 81% of all isolates. The common comorbidities were cardiovascular disease (58.7%), hypertension (57.9%), fluid electrolyte disorders (49%), sepsis (42%) and diabetes (37.5%). Overall, the mean Elixhauser weighted score was 12.1, the mortality rate was 0.9% and the ICU admission rate was 4.8%. The average number of days for

length of hospital stay was 15 days, turn-around time for the AST test was 3 days and antibiotic therapy duration was 12 days (Tables 5.1-5.5).

5.3.2. Characteristics of BDM Occurrence

There were 5,157 antibiotic orders classified as BDM therapy (7%). When compared to appropriate therapy, BDM had a higher percentage of combination antibiotic therapy (16% vs 48%; $p<0.001$), MRSA infections (14% vs 20%; $p<0.001$), polymicrobial infections (4% vs 13%; $p<0.001$), specimen collected from bone (0.7% vs 2%; $p<0.001$), cardiovascular disease (58% vs 64%; $p<0.001$), neurological disorder (21% vs 26%; $p<0.001$), renal failure (26% vs 32%; $p<0.001$), psychological disorders (31% vs 35%; $p<0.001$), anemia (14% vs 18%; $p<0.001$), higher Elixhauser weighted score (Mean; 11.9 vs 13.7; $p<0.001$); ICU admission (4.6% vs 6.3%; $p<0.001$); average duration of stay (14 days vs 19 days; $p<0.001$); average antibiotic therapy duration (17.5 days vs 22 days; $p<0.001$) (Tables 5.1-5.5).

Table 5.1. Patient characteristics

Patient Characteristics	**Appropriate (N=63282)**	**BDM (N=4689)**	**Total (N=67971)**	**p value**
Gender				< 0.001
Female	30121 (47.6%)	2109 (45.0%)	32230 (47.4%)	
Male	33161 (52.4%)	2580 (55.0%)	35741 (52.6%)	
Age Group				< 0.001
0 - 17	4857 (7.7%)	278 (5.9%)	5135 (7.6%)	
18 - 64	31576 (49.9%)	2361 (50.4%)	33937 (49.9%)	
>= 65	26849 (42.4%)	2050 (43.7%)	28899 (42.5%)	
Race				0.459
African American	12953 (20.5%)	972 (20.7%)	13925 (20.5%)	
Asian/Pacific Islander	1062 (1.7%)	92 (2.0%)	1154 (1.7%)	
Biracial	149 (0.2%)	10 (0.2%)	159 (0.2%)	
Caucasian	43366 (68.5%)	3210 (68.5%)	46576 (68.5%)	
Hispanic	734 (1.2%)	60 (1.3%)	794 (1.2%)	
Other	5018 (7.9%)	345 (7.4%)	5363 (7.9%)	

Table 5.2. Facility Characteristics

Facility Characteristics	Appropriate (N=67381)	BDM (N=5157)	Total (N=72538)	p value
Pediatric	3667 (5.4%)	219 (4.2%)	3886 (5.4%)	<0.001
Acute	67313 (99.9%)	5150 (99.9%)	72463 (99.9%)	0.453
Teaching facility	47915 (71.1%)	3727 (72.3%)	51642 (71.2%)	0.076
Urban status	55973 (83.1%)	4169 (80.8%)	60142 (82.9%)	< 0.001
Census Region				< 0.001
Midwest	10092 (15.0%)	911 (17.7%)	11003 (15.2%)	
Northeast	14015 (20.8%)	1098 (21.3%)	15113 (20.8%)	
South	30943 (45.9%)	2282 (44.3%)	33225 (45.8%)	
West	12331 (18.3%)	866 (16.8%)	13197 (18.2%)	
Bed size range				< 0.001
<5	1478 (2.2%)	78 (1.5%)	1556 (2.1%)	
6-99	3898 (5.8%)	286 (5.5%)	4184 (5.8%)	
100-199	9417 (14.0%)	636 (12.3%)	10053 (13.9%)	
200-299	17167 (25.5%)	1093 (21.2%)	18260 (25.2%)	
300-499	18163 (27.0%)	1604 (31.1%)	19767 (27.3%)	
500+	17258 (25.6%)	1460 (28.3%)	18718 (25.8%)	
Year of encounter				
2009	4210 (6.2%)	302 (5.9%)	4512 (6.2%)	< 0.001
2010	5048 (7.5%)	471 (9.1%)	5519 (7.6%)	
2011	4850 (7.2%)	391 (7.6%)	5241 (7.2%)	
2012	5798 (8.6%)	483 (9.4%)	6281 (8.7%)	
2013	7806 (11.6%)	646 (12.5%)	8452 (11.7%)	
2014	9273 (13.8%)	730 (14.2%)	10003 (13.8%)	
2015	9818 (14.6%)	739 (14.3%)	10557 (14.6%)	
2016	11485 (17.0%)	818 (15.9%)	12303 (17.0%)	

Table 5.3. Antibiotic characteristics

Antibiotics	Appropriate (N=67381)	BDM (N=5157)	Total (N=72538)
Amikacin	53 (0.1%)	2 (0.0%)	55 (0.1%)
Amox/Clav	561 (0.8%)	44 (0.9%)	605 (0.8%)
Amp/Sulb	614 (0.9%)	68 (1.3%)	682 (0.9%)
Ampicillin	861 (1.3%)	58 (1.1%)	919 (1.3%)
Aztreonam	99 (0.1%)	7 (0.1%)	106 (0.1%)
Cefazolin	3058 (4.5%)	429 (8.3%)	3487 (4.8%)
Cefepime	1483 (2.2%)	49 (1.0%)	1532 (2.1%)
Cefoxitin	89 (0.1%)	9 (0.2%)	98 (0.1%)
Ceftazidime	381 (0.6%)	19 (0.4%)	400 (0.6%)
Ceftriaxone	7323 (10.9%)	155 (3.0%)	7478 (10.3%)
Cefuroxime	92 (0.1%)	3 (0.1%)	95 (0.1%)
Ciprofloxacin	6923 (10.3%)	521 (10.1%)	7444 (10.3%)
Clindamycin	3996 (5.9%)	329 (6.4%)	4325 (6.0%)
Combination	10939 (16.2%)	2209 (42.8%)	13148 (18.1%)
Doxycycline	165 (0.2%)	3 (0.1%)	168 (0.2%)
Ertapenem	637 (0.9%)	2 (0.0%)	639 (0.9%)
Erythromycin	33 (0.0%)	33 (0.6%)	66 (0.1%)
Gentamicin	1338 (2.0%)	60 (1.2%)	1398 (1.9%)
Levofloxacin	7023 (10.4%)	789 (15.3%)	7812 (10.8%)
Linezolid	2606 (3.9%)	5 (0.1%)	2611 (3.6%)
Meropenem	1124 (1.7%)	40 (0.8%)	1164 (1.6%)
Moxifloxacin	295 (0.4%)	17 (0.3%)	312 (0.4%)
Oxacillin	700 (1.0%)	9 (0.2%)	709 (1.0%)
Pip/Tazo	3233 (4.8%)	91 (1.8%)	3324 (4.6%)
Rifampin	1108 (1.6%)	13 (0.3%)	1121 (1.5%)
Tigecycline	90 (0.1%)	1 (0.0%)	91 (0.1%)
Tobramycin	266 (0.4%)	12 (0.2%)	278 (0.4%)

Table 5.4. Microbiology pathogen and source site characteristics

Microbiology characteristics	**Appropriate (N=67381)**	BDM **(N=5157)**	**Total (N=72538)**
Pathogens			
Acinetobacter	511 (0.8%)	94 (1.8%)	605 (0.8%)
Citrobacter	715 (1.1%)	42 (0.8%)	757 (1.0%)
Enterobacter	2226 (3.3%)	280 (5.4%)	2506 (3.5%)
Enterococcus	4330 (6.4%)	513 (9.9%)	4843 (6.7%)
Escherichia	14399 (21.4%)	799 (15.5%)	15198 (21.0%)
Haemophilus	173 (0.3%)	1 (0.0%)	174 (0.2%)
Klebsiella	5396 (8.0%)	204 (4.0%)	5600 (7.7%)
MRSA	9101 (13.5%)	1022 (19.8%)	10123 (14.0%)
Polymicrobial	2754 (4.1%)	680 (13.2%)	3434 (4.7%)
Proteus	2460 (3.7%)	158 (3.1%)	2618 (3.6%)
Pseudomonas	4599 (6.8%)	272 (5.3%)	4871 (6.7%)
Salmonella	236 (0.4%)	4 (0.1%)	240 (0.3%)
Serratia	1124 (1.7%)	125 (2.4%)	1249 (1.7%)
Staphylococcus	14576 (21.6%)	837 (16.2%)	15413 (21.2%)
Streptococcus	4781 (7.1%)	126 (2.4%)	4907 (6.8%)
Source Site			
Abdomen	1671 (2.5%)	125 (2.4%)	1796 (2.5%)
Abscess	26167 (38.8%)	2439 (47.3%)	28606 (39.4%)
Blood	29967 (44.5%)	1585 (30.7%)	31552 (43.5%)
Body Fluid	3163 (4.7%)	223 (4.3%)	3386 (4.7%)
Bone	490 (0.7%)	78 (1.5%)	568 (0.8%)
Incision	2015 (3.0%)	174 (3.4%)	2189 (3.0%)

Table 5.5. Clinical characteristics and conditions

Clinical Characteristics	Appropriate (N=67381)	BDM (N=5157)	Total (N=72538)	p value
Sepsis	28449 (42.2%)	2079 (40.3%)	30528 (42.1%)	0.008
Surgery	1009 (1.5%)	98 (1.9%)	1107 (1.5%)	0.023
Cardiovascular	39246 (58.2%)	3304 (64.1%)	42550 (58.7%)	< 0.001
Diabetes	24995 (37.1%)	2238 (43.4%)	27233 (37.5%)	< 0.001
Cancer	8721 (12.9%)	669 (13.0%)	9390 (12.9%)	0.951
Hypertension	38870 (57.7%)	3161 (61.3%)	42031 (57.9%)	< 0.001
Neurological	14113 (20.9%)	1355 (26.3%)	15468 (21.3%)	< 0.001
Hypothyroidism	9535 (14.2%)	829 (16.1%)	10364 (14.3%)	< 0.001
Psychological	20928 (31.1%)	1817 (35.2%)	22745 (31.4%)	< 0.001
Anemia	9696 (14.4%)	928 (18.0%)	10624 (14.6%)	< 0.001
Renal Failure	17703 (26.3%)	1646 (31.9%)	19349 (26.7%)	< 0.001
Liver Disease	9023 (13.4%)	697 (13.5%)	9720 (13.4%)	0.8
Rheum Arthritis	4280 (6.4%)	322 (6.2%)	4602 (6.3%)	0.759
Fluid Electrolyte	33155 (49.2%)	2814 (54.6%)	35969 (49.6%)	< 0.001
Elixhauser				< 0.001
Mean (SD)	11.97 (13.12)	13.78 (13.62)	12.10 (13.16)	
Range	-18 to 78	-14 to 64	-18 to 78	
Expired	591 (0.9%)	28 (0.5%)	619 (0.9%)	0.012
ICU	3123 (4.6%)	327 (6.3%)	3450 (4.8%)	<0.001
Length of stay				< 0.001
Mean (SD)	14.432 (33.284)	19.357 (35.947)	14.782 (33.504)	
Range	0 - 2656	0 - 1504	0-2656	
Turn-around-time				0.335
Mean (SD)	2.954 (8.984)	3.074 (2.171)	2.962 (8.678)	
Range	0 - 1222	0 - 122	0 - 1222	
Antibiotic duration				< 0.001
Mean (SD)	17.523 (48.124)	22.311 (38.379)	17.863 (47.513)	
Range	0 - 5855	0 - 844	0 - 5855	

From the multiple logistic regression model, factors significantly associated with the BDM occurrence included (OR; 95% CI): patients with sepsis (1.11; 1.01-1.21); psychological disorders (1.12; 1.03-1.23); neurological disorders (1.15; 1.04-1.28); anemia (1.15; 1.03-1.27); Elixhauser weighted score (1.009; 1.003-1.015); MRSA infection (1.42; 1.06-1.91); *Enterococcus* infection (2.12; 1.57-2.90); bone as a sample source site (2.35; 1.58-3.48); ICU admission (1.32; 1.12-1.54); facilities with a bed size > 500 (1.66; 1.78-1.23); facilities with a bed size (300-499) (1.53;1.10-2.16); Asian/pacific Islander ethnicity (1.32; 0.99-1.74); adults (age 18-64) (1.69; 1.30-2.23); senior adults (age >= 65) (1.936; 1.481-2.559); encounter year 2010 (1.23; 1.01-1.50) (Figure 5.2, Table 5.6).

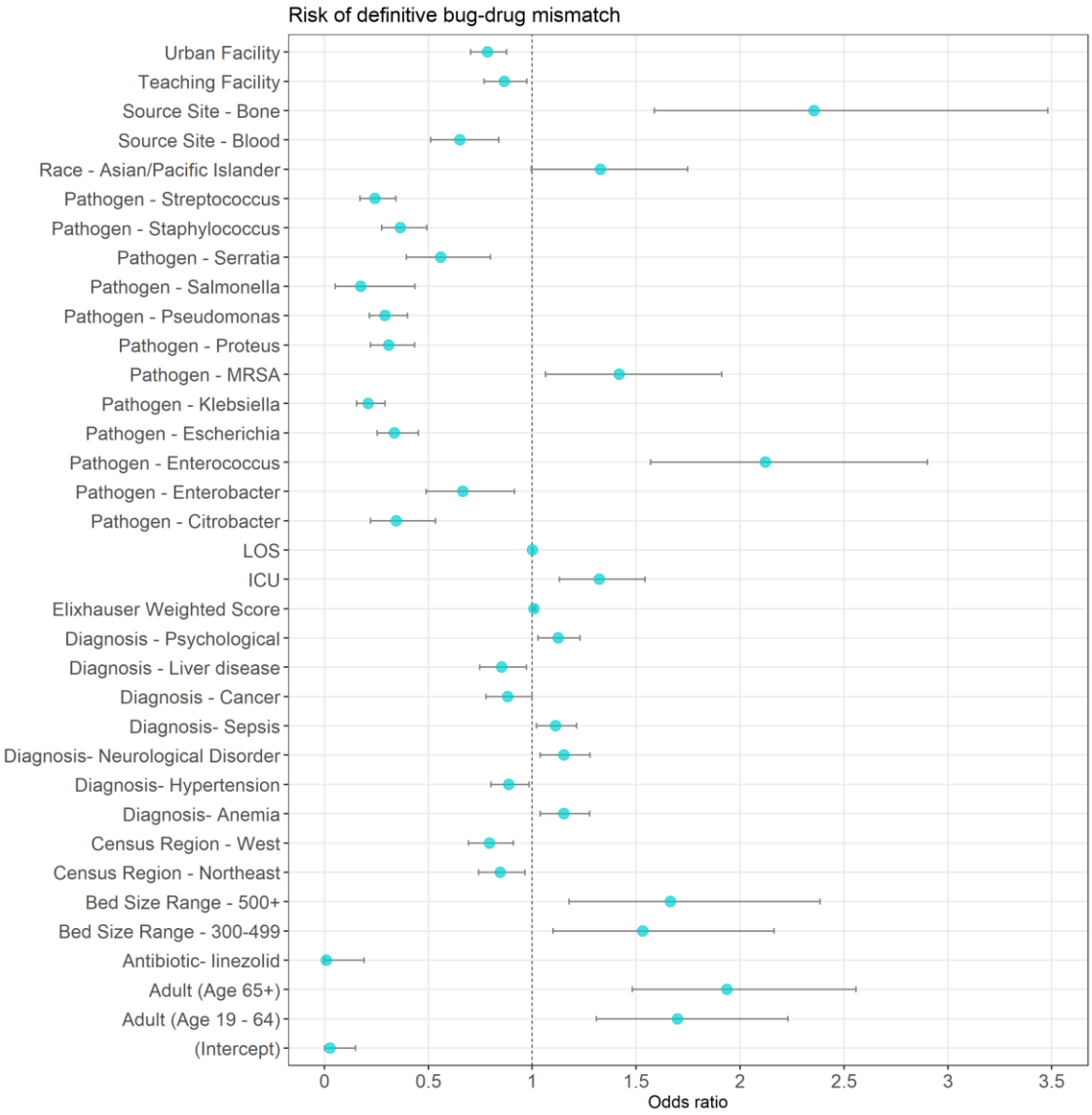

Figure 5.2. Odd ratios of significant risk factors associated with BDM therapy estimated from logistic regression model

Table 5.6. Risk factors associated with BDM therapy estimated from logistic regression model

Risk factors	OR (95% CI)	P value
Bed size range 300-499	1.532(1.1-2.164)	0.0133
Bed size range 500+	1.665(1.178-2.386)	0.0046
Race- Asian/Pacific Islander	1.328(0.996-1.748)	0.0479
Sepsis	1.112(1.02-1.212)	0.016
Elixhauser Weighted Score	1.009(1.003-1.015)	0.0043
Adult (18 -64 years)	1.699(1.309-2.23)	0.0001
Senior adults (>=65 years)	1.936(1.481-2.559)	<0.0001
Pathogen - Enterococcus	2.123(1.57-2.901)	<0.0001
Pathogen - MRSA	1.418(1.065-1.912)	0.0192
ICU	1.323(1.13-1.543)	0.0004
Length of Stay	1.001(1-1.002)	0.0045
Source Site - Bone	2.357(1.588-3.481)	<0.0001
Neurological disorder	1.153(1.038-1.279)	0.0076
Psychological disorder	1.125(1.029-1.229)	0.0096
Anemia	1.153(1.039-1.277)	0.0069

5.3.3. Prediction of BDM occurrence

The discrimination ability of different models, as represented by ROC curves, is shown in figure 5.3.

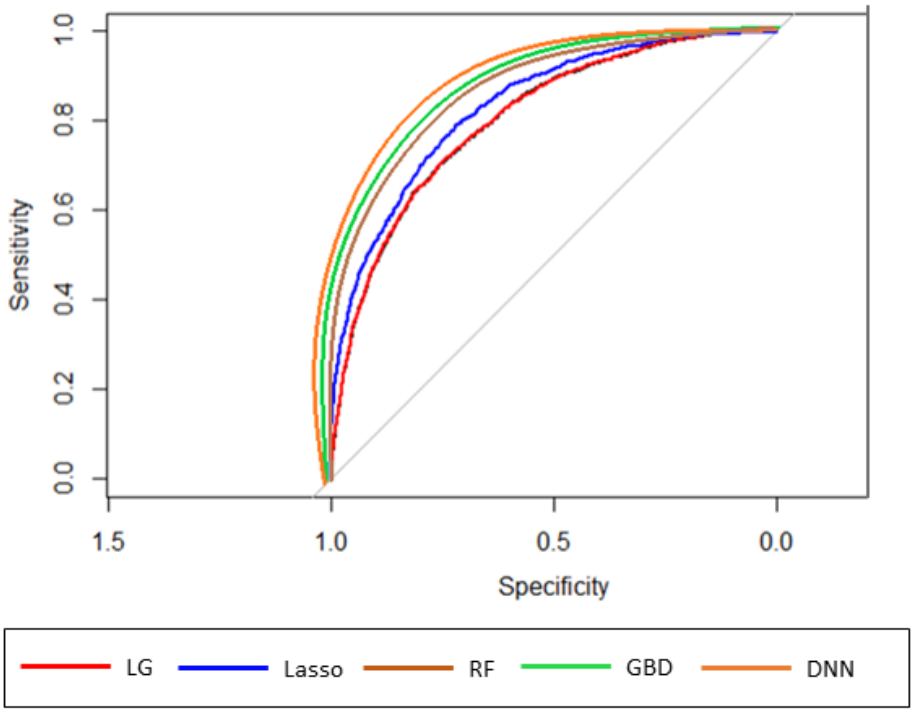

Figure 5.3. Receiver operating characteristics curves**.** Prediction ability of the reference model logistic regression (LG), logistic regression with lasso regularization (lasso), deep neural network (DNN), gradient boosted decision tree (GBD), random forest (RF) in the test set. The corresponding values of the area under the curve for each model (ie, C statistics) are presented in Table 5.7.

The reference model (logistic regression) had the lowest discriminative ability (C statistic, 0.78; 95% CI, 0.71-0.85), while all the 4 machine learning models had a higher discriminative ability. For example, the random forest model and GBD had significantly higher C statistics (random forest: 0.8364; P <0.01 and GBD: 0.8442; P < 0.01). All the machine learning had a higher accuracy than the reference model (eg, 0.899 in the reference model vs 0.9061 in the gradient boosted decision tree). Additionally, compared with the reference model, all machine learning except lasso had a higher specificity (eg, 0.37 [95% CI, 0.34-0.39] in the reference model vs 0.51 [95% CI, 0.48-0.53] in the random forest) to predict BDM occurrence. The positive predictive values (tests for BDM

occurrence outcome) of all models were high (0.95 [95% CI, 0.93-0.96] in all models) and the negative predictive values were lower (0.34 [95% CI, 0.30-0.39] in all models). Compared to the reference model, random forest model had both higher positive likelihood ratio (1.48 [95% CI, 1.43-1.54] vs 1.85 [95% CI, 1.76-1.95]) and negative likelihood ratio (0.16 [95% CI, 0.15-0.18] vs 0.17 [95% CI, 0.16-0.19]) (Table 5.7).

Table 5.7. Prediction ability of the reference model and 4 machine learning models

Model	C statistic	P-value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR	NLR	Accuracy
LR	0.8049	Ref.	0.94 (0.93-0.95)	0.37 (0.34-0.39)	0.95 (0.93-0.96)	0.32 (0.30-0.34)	1.48 (1.43-1.54)	0.16 (0.15-0.18)	0.8990
Lasso	0.8057	0.27	0.94 (0.92-0.95)	0.36 (0.34-0.39)	0.95 (0.93-0.96)	0.33 (0.30–0.35)	1.48 (1.43-1.54)	0.16 (0.15-0.17)	0.9000
DNN	0.845	0.003	0.93 (0.94-0.95)	0.44 (0.39-0.48)	0.95 (0.93-0.96)	0.35 (0.34-0.37)	1.69 (1.56-1.73)	0.18 (0.14 – 0.19)	0.9010
GBD	0.8442	0.005	0.94 (0.94-0.95)	0.42 (0.40-0.45)	0.95 (0.95-0.96)	0.37 (0.35-0.39)	1.64 (1.57-1.71)	0.13 (0.12-0.14)	0.9061
RF	0.8364	0.025	0.91 (0.91-0.92)	0.51 (0.48 – 0.53)	0.96 (0.96-0.96)	0.31 (0.29-0.33)	1.85 (1.76-1.95)	0.17 (0.16-0.19)	0.9001

Reference (Ref.) model; Logistic regression (LG); logistic regression with lasso regularization (lasso); deep neural network (DNN); gradient boosted decision tree (GBD); random forest (RF)

5.3.4. Variable impact in ML models

Figure 5.4 demonstrates the impact of the variables in random forest and gradient boosted decision tree.

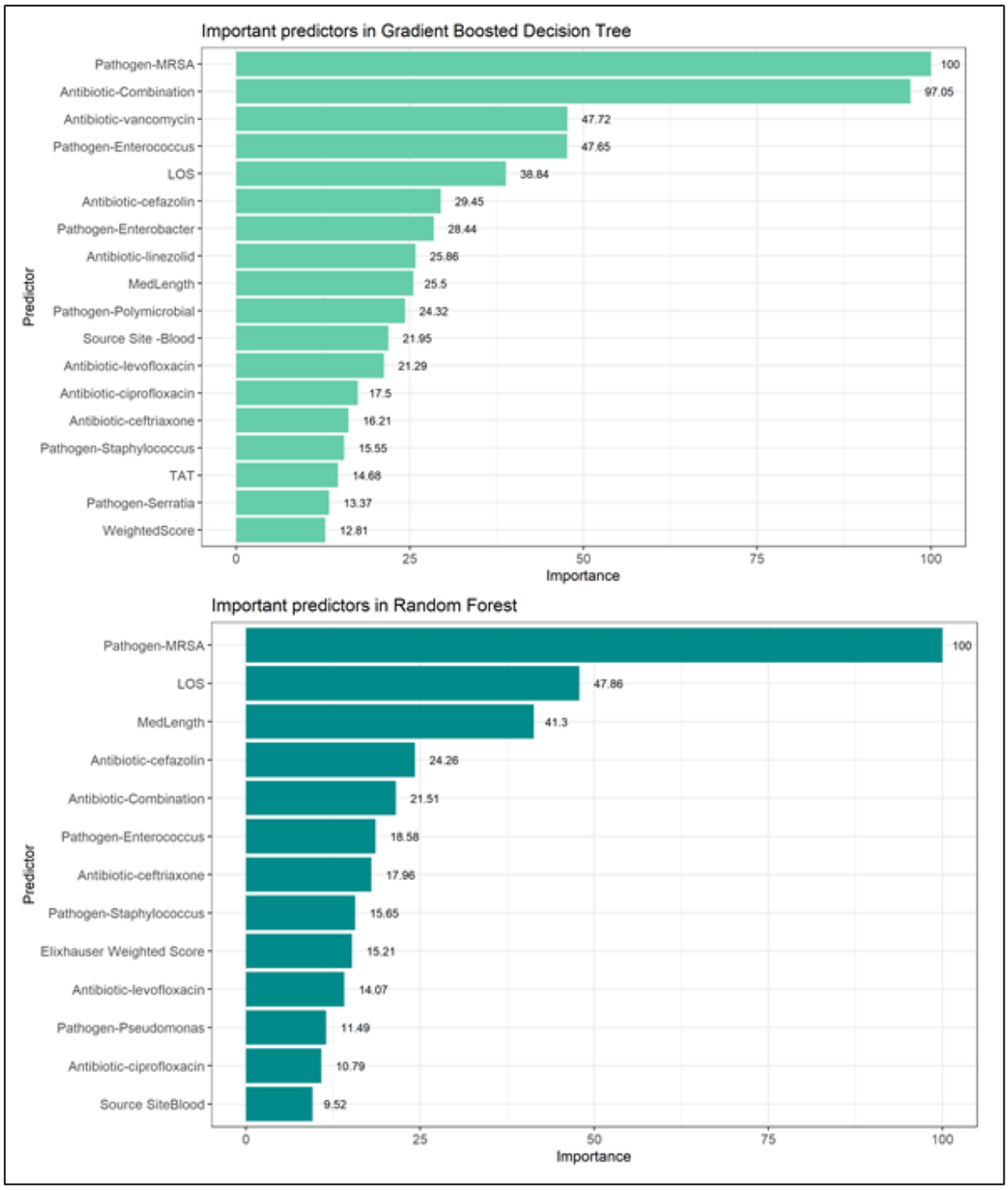

Figure 5.4. Importance of Each Predictor in the Gradient-Boosted Decision Tree Models and Random Forest models. The variable importance is a measure scaled to have a maximum value of 100.

In both the models, MRSA infection, blood as a source site, length of stay, duration of antibiotic therapy, combination antibiotic therapy, cefazolin and ciprofloxacin therapy were important predictors.

5.4. Discussion

In this analysis of nationally representative data of antibiotic orders and AST test results, we were able to identify significant risk factors for BDM occurrence and we applied machine learning approaches (ie, lasso regression, random forest, gradient-boosted decision tree, and deep neural network) to improve the overall discrimination ability to predict BDM occurrence based on machine learning prediction metrics.

In our study we noted that adults (age 18-64) were 69% more likely and senior adults (age > 65) were 93% more likely to have a BDM than children. Our finding indicates that the age group of the patient has a significant impact on the appropriateness of the antibiotic therapy. This finding is probably due to the differences in antibiotic need and use between children and adults (17, 18). Antimicrobial adverse effects also differ between children and adults (105, 106).

Our study noted a significant association between complex patient conditions and the risk of BDM occurrence. Patients with sepsis were 11% more likely of receiving a BDM. Studies on sepsis have shown that inappropriate antibiotics or delayed administration of antibiotics is associated with detrimental outcomes (229–231). Patients with anemia were 15% more likely, patients with psychological disorders were 12% more likely and patients with neurological disorders were 15% more likely to receive a BDM. Several studies have explored the psychiatric adverse effects of antibiotics where early life exposure antibiotics have been associated with elevated risk of some psychiatric

disorders. Managing BDM occurrence could reduce the incidence of these sequelae (234, 235). Additionally, the odds of receiving a BDM increases by 9% with every unit increase in the weighted Elixhauser score. Several studies have examined the importance of comorbidity associated with inappropriate antibiotic use (236–238). Our study also identifies patients in an ICU were 32% more likely to have a BDM. This finding is consistent with other work indicating that 30% to 60% of antibiotics prescribed in ICUs are unnecessary, inappropriate, or suboptimal (239, 240). ICU's have a disproportionately high incidence of difficult to treat AR infections where patients may receive the incorrect antibiotic as a salvage therapy (241, 242). Appropriate antibiotic stewardship in ICUs should include rapid identification and optimal treatment of bacterial infections by improving the ability to avoid BDM. Another potential factor in our study was patients with MRSA infection were 41% more likely to have a BDM. This is possible due to the widespread prevalence of multi-drug resistance and pan-drug resistance in MRSA infections (61). This finding can also be related to the increasing evidence that inappropriate antibiotics not only encourage overgrowth with MRSA but may also enhance pathogenicity (243).

Another significant risk factor was patients from larger facilities (bed size greater than 500), were 66% more likely and facilities with bed size between 300-500 were 53% more likely to have a BDM than small ambulatory clinics (bed size < 5). This finding parallels findings from several studies which reported variation in inappropriate antibiotic ordering among and within different health care settings (244, 245).

Although we were not able to include individual provider characteristics in our study, other work has noted that cultural factors (such as patient attitudes) and external

forces (such as insurance type, accessibility and price of antibiotics, or public opinion) may influence the prescribing of antibiotics (246, 247). Prior studies suggest that provider beliefs stemming from the number of years of experience and method of training factor into the decision to prescribe antibiotics, and that the providers have individual treatment styles regardless of patient characteristics (248, 249). Another study found that resident physicians had lower rates of antibiotic ordering than attending physicians, which may reflect an impact of trainee education regarding antimicrobial stewardship. Other local factors, such as the culture within each provider's practice, may contribute to the decision-making process in prescribing an antibiotic (250). Providers within a clinic may coalesce around prescribing practices, especially if they share patients who have expectations about receiving antibiotics in particular situations. These differences in prescribing behavior among providers and clinics may offer targets for future interventions. Further research is needed to characterize antibiotic prescribing patterns for patients managed in these settings as this likely represents an important, yet under recognized, area of consideration in attempts to improve antibiotic stewardship.

The findings reported in this study are critical in designing antibiotic stewardship efforts such as clinical decision support system tools which provide BDM alert focused on the age group of the patients to prevent BDM and improve patient outcomes (24, 25). We recommend tailoring these interventions to specific patient characteristics, patient comorbidities, settings of care and provider types which could be more effective in improving appropriate prescribing and ultimately improving patient outcomes as well as reducing antibiotic resistance. Additionally, future national stewardship efforts should target education and antimicrobial stewardship interventions for advanced practice

providers, as their role continues to grow (109). Educational interventions may include dissemination of susceptibility information, use of computer-based algorithms, and academic detailing. An understanding of the factors contributing to potentially inappropriate antibiotic use can help guide policy makers to design an effective educational or administrative intervention. Several CDSS tools have been developed recently using machine learning techniques such as the ability to recommend initial treatment for patients with hepatocellular carcinoma, to identify prescriptions with a high risk of medication error and to optimize medication therapies for Parkinson's disease (119, 251, 252). The increasingly widespread availability of electronic health records and the development of big data analytics are currently paving the way for the use of machine learning techniques, which relies on sophisticated algorithms with the capacity to analyze vast quantities of data to identify potential medical problems (253).

The machine learning models implemented in this study achieved higher predictive performance to identify BDM occurrence compared to standard LR methods. These machine learning models also achieved a higher sensitivity (identify patients with BDM occurrence), higher specificity (identify patients with appropriate therapy), higher positive predictive value (proportion of patients predicted with BDM who actually had the BDM), higher negative predictive value (proportion of patients predicted with appropriate antibiotics therapy who actually had appropriate therapy), higher positive likelihood ratio (increase in the odds of having a BDM in patients who are predicted to have a BDM), negative likelihood ratio (increase in the odds of having an appropriate therapy in patients who are predicted to have an appropriate therapy).

There are several potential explanations for the incremental gains in the prediction ability by the machine learning approaches. First, machine learning approaches are able to incorporate the high-order nonlinear interactions between predictors, which cannot be addressed by traditional modeling approaches (eg, logistic regression model) (211). Additionally, we applied rigorous approaches to minimize potential overfitting of the models (eg, lasso and ridge regularization, cross-validation, and dropout). Modern machine learning approaches possess scalability within a larger context of health information technology (eg, extracting a multitude of potential predictors from electronic health records and monitoring devices, continuous sophistication of the model using updated health data, and reinforcement learning) (254). This is the first study that has identified risk factors specifically for BDM occurrence and implemented machine learning models to predict BDM occurrence.

Our study has several potential limitations. First, we were not able to account for provider level characteristics in our model factor in IAAT. Second, we excluded encounters with no information on the AST testing, a potential source of selection bias. Third, the machine learning approaches are data driven and, therefore, depend on accurate and complete data. Variations in the coding and accuracy of the EHR data are well known, a potential source of bias in the machine learning models. Fourth, the imputation of missingness is a potential source of bias, even though, random forest is known to be a rigorous technique for imputation.

In conclusion, by using large scale de-identified EHR data we were able to identify several significant risk factors associated with BDM occurrence. Primary risk factors such as age of the patient, patient comorbidities and care setting are critical to

expand antibiotic stewardship efforts into these settings to reduce BDM occurrence. Additionally, the machine learning models developed in our study has a high predictive ability, higher sensitivity, PPV and PLR to identify BDM than the reference model which could be used to develop CDSS tools as part of ASP efforts to reduce BDM occurrence as a measure of improving appropriate prescribing which ultimately results in improving patient outcomes and reducing antibiotic resistance.

CHAPTER 6

CONCLUSION

6.1. Significance of Findings

Antibiotic resistance in bacteria continues to evolve and represent an ever-increasing danger in all populations, including children. The potential for negative patient outcomes increases as AR becomes more prevalent. The high economic burden in the healthcare sector has become a burning issue, due to extended hospital stays, isolation wards, stringent infection control measures and treatment failures. Opportunities to mitigate spread of these dangerous organisms are numerous, and multi-faceted approaches should focus on education and training, bundled infection prevention measures, antibiotic stewardship programs, and addressing modifiable risk factors for infection. A heightened awareness and targeted resources by national and international programs, especially those dedicated to the health of children, are essential to halt the spread of these menacing pathogens in our most vulnerable population.

We observed several statistically significant changes in AR rates over time with respect to age and care-setting. The examples discussed in the study highlight the growing problem of bacteria developing resistance to first line therapies. These trends are especially concerning for providers, as they are often the first point of contact for patients presenting with these diseases and must determine which antibiotics to administer. Failure to identify and properly treat these organisms can have a devastating impact on

patient outcomes. As such, it is important for providers to review previous culture and sensitivity results when available, particularly in patients with risk factors for resistant organisms. One important strategy to combat AR is to consider the emerging trend in AR and factoring the age of the patient while implementing care-setting specific ASP to optimize antibiotic use, reduce healthcare cost and improve patient outcomes.

One proposed method of attenuating the rise of resistance is reducing unnecessary antibiotic use such as BDM. We found that the BDM prevalence for several critically important antibiotics differed between children and adults as well as within pediatric and blended facilities. We were also able to identify several significant risk factors associated with BDM occurrence. Primary risk factors such as age of the patient, patient comorbidities and care setting are critical to expand antibiotic stewardship efforts into these settings to reduce BDM occurrence. Additionally, the machine learning models developed in our study has a high predictive ability, higher sensitivity, PPV and PLR to identify BDM than the reference model which could be used to develop CDSS tools as part of ASP efforts. These efforts to reduce BDM occurrence as a measure of improving appropriate prescribing would ultimately result in improving patient outcomes and reducing antibiotic resistance.

6.2. Strengths and Limitations

Our work has known limitations. First, despite controlling for the total number of encounters, confounding variables for severity of resistance may exist. However, this does not change our result with respect to the proportion of baseline resistance or trend in resistance. Second, it could not be ascertained whether the infections were community acquired or nosocomial or whether resistance was primary or secondary, the AR rates

were generalized to the full study population. Third, our work is observational and does not provide insights into the drivers for the changes in AR patterns. Fourth, our work was retrospective using a de-identified data resource, there is no way to determine whether the choice of antibiotics for the study population were confounded by factors beyond our recognition. Fifth, we were not able to account for provider level characteristics in our model to predict BDM which had been identified as potential risk factor in inappropriate antibiotic therapy. Sixth, we excluded encounters with no information on the AST testing, which might be a potential source of selection bias. Seventh, the machine learning approaches are data driven and, therefore, depend on accurate data. Variations generally exist in the coding and accuracy of the EHR data, which introduces bias in the machine learning models. Eighth, the imputation of missingness by random forest is a rigorous technique yet is a potential source of bias.

Our study also had several strengths. We describe the first use of large scale EHR data to identify difference in the trends in resistance within care-setting. Second, our data has representation of different regions in the US and a large sample size, which reduces biases of local origin, increases external validity and provides statistical power. Third, we used powerful data visualization techniques to discern patterns, identify linear relationships in 302 pathogen-antibiotic pairs, repeat the analysis for four groups and focus on significant insights readily apparent in the MCS and C-MCS plots. Fourth, we validated the accuracy of the HF data source for the first time with internal antibiogram data. Fifth, we evaluated BDM at 217 US healthcare facilities from 64 non-affiliated organizations, in contrast to other work which is from a single institution or smaller number of organizations. Sixth, the data source combines laboratory, medication,

surgery, patient diagnosis and facility characteristics which made it possible to evaluate risk factors for BDM occurrence. Seventh, this is also the first study that has implemented machine learning models to predict BDM occurrence by incorporating the high-order nonlinear interactions between predictors, which cannot be addressed by traditional modeling approaches.

6.3. Future Work

Future studies include several corrective measures to target the growing problem of antibiotic resistance. Including provider level characteristics as additional predictors might further improve the accuracy of the ML models to predict BDM occurrence. Implementing the ML algorithm to develop clinical decision support systems as part of the ASP initiative to automatically identify BDM occurrences and streamline antibiotic therapy for patients will improve appropriate prescribing and ultimately result in improving patient outcomes and reducing antibiotic resistance. Additionally, widespread implementation of care-setting specific ASP which factors the age group of the patient will be pivotal to combat the rising threat of AR infections.

In conclusion, the findings reported in this study on the trends of AR, prevalence and risk factors of BDM are critical in tailoring antibiotic stewardship efforts to improving appropriate antibiotic prescribing and to ultimately reduce AR.

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VITA

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