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Trends In Antibiotic Resistance And Correlations Of Antibiotic Use And Antibiotic Resistance In A Small Hospital In El Paso, Texas 2013-2015

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Dedication

I would like to dedicate this work to my family who have always been there for me and have supported me, in every way possible, throughout my professional and personal life.

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by

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THESIS

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Abstract

Antibiotic resistance is a serious public health threat, primarily, resulting from the excess and inappropriate use of antibiotics. Antibiotic resistance and antibiotic consumption trends may differ along the U.S-Mexico border from the rest of the U.S. due to geographical and cultural differences unique to the border region. The objectives of this study were: 1.) To examine the trends in antibiotic resistance among *E. coli*, ESBL producing *E. coli*, *P. aeruginosa*, *S. aureus*, and MRSA over a 3-year period (2013, 2014, 2015) in a U.S.-Mexico border area hospital; 2.) To examine the trends in antibiotic consumption among aztreonam, cefazolin, cefepime, ceftriaxone, ciprofloxacin, gentamicin, and levofloxacin over a 3-year period (2013, 2014, 2015) in a U.S.-Mexico border area hospital; 3.) To determine if a correlation exists between the consumption of these antibiotics and antibiotic resistance trends seen in a U.S.-Mexico border area hospital. This study employed a retrospective analysis of antibiotic resistance and antibiotic consumption data in a small border area hospital in El Paso, Texas to determine if a correlation existed between the two variables for the time-period of 2013-2015. The results of this study identified statistically significant increases in resistance for *E. coli* to aztreonam (p-value <0.0001), cefazolin (p-value <0.0001), cefepime (p-value <0.0001), ceftriaxone (p-value <0.0001), and ciprofloxacin (p-value 0.001). A statistically significant increase in resistance for MRSA to gentamicin was also identified (p-value 0.044). Statistically significant decreases in resistance were identified for ESBL producing *E. coli* to gentamicin (p-value 0.002) and for *S. aureus* to the following antibiotics: ciprofloxacin (p-value 0.023), levofloxacin (p-value 0.018), and penicillin (p-value 0.021). No correlations were identified between any of the susceptibilities of the bacterial species and the antibiotic consumption data analyzed.

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Chapter 1: Introduction

The discovery of antibiotics has been one of the world's most revolutionizing discoveries of the modern era. Since the discovery of penicillin in the late 1920s, antibiotics have saved millions of lives (Centers for Disease Control and Prevention, 2013) through curing, previously, incurable illnesses. In addition, antibiotics have played a significant role in the prevention of surgical site infections when distributed as a prophylactic (McHugh, Collins, Corrigan, Hill, & Humphreys, 2011). Despite the advances antibiotics have made in improving the lives of millions of people, they have also, paradoxically, indirectly contributed to the mortality and morbidity of hundreds of thousands of lives.

Antibiotic resistance is a serious public health threat throughout the globe. Antibiotic resistance occurs when bacteria are able to survive in the presence of antibiotics without effect. Antibiotic resistance can be innate or acquired. With innate resistance, all strains of a bacterial species are naturally resistant to a class of antibiotics (Tenover, 2006). Acquired resistance occurs when bacteria become less susceptible to antibiotics that were once effective against them through the selective pressures of antibiotic use (Tenover, 2006). This differs from innate resistance in that acquired resistance traits are only found in some strains or subpopulations of a bacterial species (Michigan State University, 2011).

There is limited data on antibiotic resistance and antibiotic consumption along the U.S.-Mexico border. Due to various geographical and cultural differences that are unique to the U.S.-Mexico border region and population, antibiotic resistance and consumption trends may differ from those of the rest of the U.S. It is therefore essential to track antibiotic resistance and antibiotic consumption in this unique region.

Chapter 2: Background and Significance

Mechanisms of antibiotic resistance

There are four main antibiotic resistance mechanisms by which bacteria resist the effects of antibiotics (Figure 1). The first mechanism involves preventing antibiotic access to its target by reducing its ability to penetrate a cell (Michigan State University, 2011). In this mechanism, changes in the outer membrane permeability of a bacterial cell occur, such as lacking the expression of a porin protein needed for antibiotic entry into the cell. Imipenem resistant *P. aeruginosa*, as an example, lacks the OprD porin required for entry of this antibiotic into the cell (Cloete, 2003). The second mechanism involves the acquisition of general or specific efflux pumps to expel antibiotics from the cell (Michigan State University, 2011). This mechanism prevents antibiotics from reaching the intracellular concentrations needed to have an effect on the bacterial cell (Michigan State University, 2011). Efflux pumps contribute significantly to multidrug resistance as most efflux pumps are multidrug pumps capable of expelling a variety of antibiotic classes from the cell (Giedraitiene, Vitkauskiene, Naginiene, & Pavilonis, 2011). The MepA efflux pump of *S. aureus*, as an example, is responsible for resistance to tigecycline, minocycline, tetracycline, ciprofloxacin, norfloxacin, ethidium bromide, and tetraphenylphosphonium bromide (Giedraitiene et al., 2011). The third mechanism involves inactivating the antibiotic through modification (Michigan State University, 2011). A common mode of inactivation occurs through the use of enzymes. Extended-spectrum beta-lactamases (ESBL) are enzymes that hydrolyze beta-lactam antibiotics rendering them ineffective. Extended-spectrum beta-lactamases are capable of inactivating penicillins; first, second, and third generation cephalosporins, and aztreonam, however, they do not have an effect on the cephamycins or carbapenems (Rawat & Nair, 2010). Extended-spectrum beta-lactamase producing *E. coli* is a

serious health threat and a common cause of hospital acquired infections. The fourth resistance mechanism involves modifying the antibiotic target site within the bacterial cell (Michigan State University, 2011). Penicillin binding proteins (PBPs), as an example, are the target site for beta-lactam antibiotics. The acquisition of altered PBPs in *S. aureus* (PBP2a) demonstrates reduced affinity for beta-lactam antibiotics and allows cell wall synthesis to occur even in the presence of normally lethal concentrations of beta-lactam antibiotics (Lim & Strynadka, 2002). All of these mechanisms of resistance are obtained genetically either through random mutation as seen with innate resistance, or through horizontal gene transfer associated with acquired resistance.

Horizontal gene transfer occurs via transformation, transduction, or conjugation. Transformation involves the uptake of naked deoxyribonucleic acid (DNA) that has been released by bacteria into the environment after cell lysis and the incorporation of the resistant genes into the host's genome (Tenover, 2006). Transduction involves the transfer of resistant genes from one bacterium to another by bacteriophages (Tenover, 2006). Conjugation involves the transfer of resistant genes from cell-to-cell contact via the pilus (Michigan State University, 2011). In all cases of acquired resistance, the selective pressure of antibiotic use leads to the acquisition of resistant genes and the proliferation of resistant bacteria.

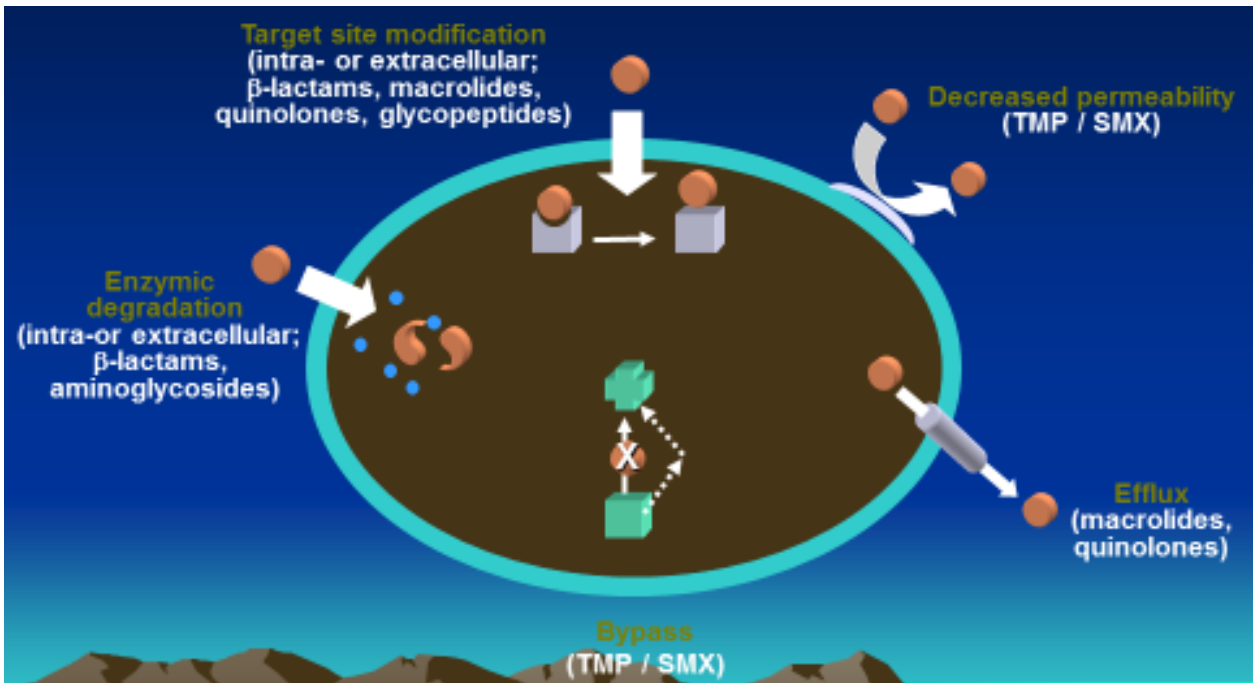

Figure 1: Mechanisms of Antibiotic Resistance. Reprinted with permission from J. O. Rivera, 2018.

Excess use of antibiotics

Selective pressures such as the inappropriate and excess use of antibiotics in a hospital and outpatient setting are believed to be the major facilitators of the growing resistance trend (Canton, Horcajada, Oliver, Garbajosa, & Vila, 2013; Fleming-Dutra et al., 2016). Globally, antibiotic use has increased by 36% between the years 2000 and 2010 with a large absolute increase in consumption seen with the cephalosporins, broad-spectrum penicillins, and fluoroquinolones (Van Boeckel et al., 2015). Total antibiotic use in the U.S. hospital setting has not changed significantly during the last decade, however, the use of broad spectrum antibiotics has increased significantly (Baggs, Fridkin, Pollack, Srinivasan, & Jernigan, 2016). Similar findings are observed when examining U.S. outpatient antibiotic use. In concordance with antibiotic use in a hospital setting, broad spectrum antibiotic use has also increased significantly in the outpatient setting (Lee et al., 2014). Estimates of inappropriate antibiotic use varies globally. Overall, global estimates of

inappropriate antibiotic use ranges from 30% up to 81% (Fleming-Dutra et al., 2016; Hatam, Askarian, Moravveji, & Assadian, 2011; Ingram, Seet, Budgeon, & Murray, 2012). Recent studies documenting inappropriate antibiotic use in the U.S. hospital setting are rare. It has been well accepted, however, that up to 50% of antibiotics prescribed in the U.S. hospital setting are inappropriate (Dellit et al., 2007; Hecker, Aron, Patel, Lehmann, & Donskey, 2003). Hecker et al. in 2003 estimated that 28% of antibiotic use in a U.S. hospital setting were inappropriate (Hecker et al., 2003). This estimate correlates well with a recent study demonstrating that 30% of antibiotic use in the U.S. outpatient setting is inappropriate (Fleming-Dutra et al., 2016). Contributing to the excess use of antibiotics are various factors such as physician response to patient pressures, diagnostic uncertainty among physicians, and self-medication among the general population.

Physician response to patient pressures in prescribing antibiotics are evident in the outpatient setting. Qualitative studies have identified patient pressure as a major barrier to the judicious use of antibiotics (Dempsey, Businger, Whaley, Gagne, & Linder, 2014; Szymczak, Feemster, Zaoutis, & Gerber, 2014). Patient expectation of antibiotic prescriptions is perceived as a general norm among physicians and studies have indicated that physicians sometimes submit to these expectations to appease patients (Szymczak et al., 2014). Additionally, studies have identified that physicians also feel that time constraints are a barrier to resolving patient misconceptions regarding antibiotic use. Physicians may be compelled to prescribe antibiotics as opposed to educating patients on appropriate use in order to end patient visits quicker and increase financial productivity (Dempsey et al., 2014). Diagnostic uncertainty also contributes to the over prescription of antibiotics. Qualitative studies have indicated that diagnostic uncertainty is a concern among physicians and can lead to prescribing antibiotics to avoid undertreating an infection (Dempsey et al., 2014; May et al., 2014). This concern highlights the need for improved

rapid and accurate point-of-care diagnostic tests. Non-prescription use or self-medication is another contributor to the excess use of antibiotics. The prevalence of non-prescription antibiotic use varies among different populations. Past studies have documented non-prescription antibiotic use primarily among Latin American immigrants (Zoorob, Grigoryan, Nash, & Trautner, 2016). The prevalence of non-prescription antibiotic use among this population ranges from 19-26% (Zoorob et al., 2016). In another study, the prevalence of non-prescription antibiotic use among a diverse population group in the state of Texas in the U.S. was lower (5%) (Zoorob et al., 2016). In this study, however, 25.4% of respondents indicated willingness to use antibiotics without a prescription and 14.2% indicated they had antibiotics stored at home (Zoorob et al., 2016). In both studies, the most common indications for non-prescription antibiotic use was for symptoms of upper respiratory illnesses, which are most likely caused by viruses.

Antibiotics are also commonly used in food animals. Previous data documents that 16% of all lactating cows in the U.S. receive therapeutic antibiotics for mastitis annually and approximately 100% of lactating cows receive prophylactic antibiotics after each lactation (Landers, Cohen, Wittum, & Larson, 2012). Additionally, 42% of beef calves and 88% of swine for food consumption receive prophylactic antibiotics (Landers et al., 2012). Antibiotic consumption in food animals varies with past estimates of total antibiotic use in the U.S. as high as 24.6 million pounds attributed to animal prophylactic use compared to 3 million pounds for human use (Landers et al., 2012). Many of the prophylactic antibiotics used in animals are also used to treat human disease such as tetracyclines, penicillins, and sulfonamides (Landers et al., 2012). The consequences of antibiotic use in animals and subsequently humans are both direct and indirect. Increased risk of resistant colonization or infection in humans results from farm animal exposure to antibiotic treated animals (Landers et al., 2012). Outbreaks of diarrheal disease

can result from the consumption of food contaminated with antibiotic-resistant bacteria (Landers et al., 2012). Antibiotic contaminated meat products can also stimulate resistance in the gut microbiome through consumption (Landers et al., 2012). Indirectly, antibiotic-resistant bacteria in animals can spread to humans through animal transport, from animal waste contaminating the water supply and through contact with pet animals exposed to antibiotic-resistant-containing pet food (Landers et al., 2012).

Consequences of excess antibiotic use

Antibiotics are not without their side effects and inappropriate and excess use puts individuals at risk of developing resistant infections or other adverse events. It is estimated that 2 million people a year in the U.S. develop serious bacterial infections with bacteria that is resistant to at least one of the antibiotics designed to target the bacteria (Centers for Disease Control and Prevention, 2013). Mortality related to these infections is estimated at 23,000 deaths a year (Centers for Disease Control and Prevention, 2013). In addition to these infections approximately 250,000 people yearly require care for *Clostridium difficile* infections (CDI) which largely occurs as a result of antibiotic use leading to a disruption of the gut microbiome (Centers for Disease Control and Prevention, 2013). Several antibiotic resistance patterns have emerged since the introduction of antibiotics, however, antibiotic resistance patterns among gram-negative bacteria are a main concern. Gram-negative bacteria are becoming resistant to almost all antibiotics used to treat these pathogens (Centers for Disease Control and Prevention, 2013). Additionally, mortality rates among hospitalized patients with multidrug-resistant gram-negative bacteria ranges from 30-70% (Tamma, Cosgrove, & Maragakis, 2012). Carbapenem-resistant Enterobacteriaceae (CRE) is a current urgent public health threat. It is estimated that 140,000 healthcare-associated Enterobacteriaceae infections occur in the U.S. annually and approximately 9,300 are caused by

CRE (Centers for Disease Control and Prevention, 2013). Up to half of blood stream infections caused by CRE result in death (Centers for Disease Control and Prevention, 2013). Extended-spectrum beta-lactamase producing Enterobacteriaceae and multidrug-resistant *P. aeruginosa* are responsible for a combined 32,000 and 2,100 annual healthcare-associated infections and deaths respectively (Centers for Disease Control and Prevention, 2013). Among gram-positive bacteria, methicillin-resistant *S. aureus* (MRSA) is a serious public health threat as this species is the leading cause of healthcare-associated infections in the U.S. (Centers for Disease Control and Prevention, 2013). Methicillin-resistant *S. aureus* is often multidrug-resistant and accounts for approximately 80,461 severe infections and about 11,285 deaths per year (Centers for Disease Control and Prevention, 2013). Total attributable societal and medical costs for antibiotic resistant infections is difficult to calculate but has been estimated as high as 55 billion dollars a year (2008 dollars) (Centers for Disease Control and Prevention, 2013).

Mitigation of antibiotic resistance

The medical and economic consequences of antibiotic resistance can be mitigated, however, through the prudent use of antibiotics such as with the implementation of antimicrobial stewardship programs (ASPs). Antimicrobial stewardship programs serve as a tool to combat antibiotic resistance. Antimicrobial stewardship programs aim to reduce the inappropriate use of antibiotics through various interventions designed to promote the judicious use of antibiotics. An increasing body of evidence exists supporting the use of these programs. These programs can optimize the treatment of infections while reducing a number of adverse events associated with antibiotic use such as: reducing treatment failures, reducing the incidence of CDI, and reducing the incidence of antibiotic resistant infections (Centers for Disease Control and Prevention, 2014). In response to the evidence of the benefits of ASPs, the Centers for Disease Control and Prevention

(CDC) now recommends that all acute care hospitals implement ASPs in an effort to quell antibiotic resistance and improve patient outcomes. Hospital antimicrobial stewardship programs have been shown to decrease resistance among many pathogens of clinical relevance (Kaki et al., 2011). Additionally, hospital ASPs have also demonstrated other favorable outcomes such as reducing the incidence of CDI, and hospital-associated vancomycin-resistant enterococci infections (Nowak, Nelson, Breidenbach, Thompson, & Carson, 2012; Wenisch et al., 2014). Although data on outpatient ASPs is limited, Dantes et al. (2015) estimated that a reduction of outpatient antibiotic prescribing rates by 10% would lead to a 16.8% overall decrease in community-associated CDI rates (Dantes et al., 2015). This indicates that outpatient ASPs may be helpful to mitigate the adverse effects associated with inappropriate antibiotic use.

U.S.-Mexico border region

The U.S.- Mexico border is roughly 2000 miles long and spans 62.5 miles to the south and north of the international border and across four U.S. and six Mexican states. The U.S.-Mexico border is a unique geographical and cultural setting with a large bi-national population and approximately 200 million passenger and pedestrian crossings in 2016 (Bureau of Transportation Statistics, 2017). Additionally, highly impoverished settlements, known as "colonias," are present in the border region and it is estimated that approximately 400,000 inhabitants occupy these "colonias" (Mier et al., 2008). In general, approximately 25% of U.S. border residents live below the federal poverty level compared to 15% for the entire U.S. (The AIDS Education and Training Center, 2014). Border residents face unique challenges in relation to healthcare. The Texas border region, for example, has poverty rates that are approximately 14% higher than the rest of the U.S. (Texas Department of State Health Services, 2013). Additionally, there are high rates of uninsured among Texas border residents. Among Texas border residents, the rate of uninsured was 34.0%

compared to 14.5% for the entire U.S. in 2013 (Barnett & Berchick, 2017; Texas Department of State Health Services, 2013). The Texas border region is also a medically underserved area with only six public health departments serving the 32 border counties in Texas and over half of the border counties have no hospital (The AIDS Education and Training Center, 2014). In El Paso, Texas, the poverty rate is at approximately 23% (Texas Department of State Health Services, 2013) and approximately 30% of residents are uninsured (Texas Medical Association, 2017). Factors such as poverty and the lack of health insurance have forced border residents to utilize healthcare services across the border in Mexico. One study estimated healthcare utilization in Mexico among Texas border residents at 49% for the purchasing of medicines and approximately 37% for physician visits (Su, Pratt, Stimpson, Wong, & Pagán, 2014).

Surveillance data on antimicrobial resistance and consumption is limited in the U.S.-Mexico border region. Due to differences in the accessibility of antibiotics in Mexico, overuse leading to increased antibiotic resistance is a major concern among border communities (Homedes & Ugalde, 2012). One study, conducted on a convenience sample of Mexican pharmacies, documented 83% of antibiotics purchased by U.S. residents from Mexican pharmacies were purchased without a prescription and were self-prescribed (Homedes & Ugalde, 2012). This same study also documented several concerning pharmacy practices in Mexico. Among U.S. and Mexican residents who purchased antibiotics from Mexican pharmacies during this study period, 57% purchased antibiotics without a prescription as recommended by the pharmacy clerk (Homedes & Ugalde, 2012). Additionally, 82% of these clerks only achieved a secondary education and their training and knowledge of medications comes largely from pharmaceutical representatives (Homedes & Ugalde, 2012). Although published antibiotic resistance data in the border region is rare, one study documented a higher prevalence of MRSA in El Paso, Texas when

compared to its Mexican counterpart, Ciudad Juarez (Rivera et al., 2009). Another study documented statistically significant increasing trends in resistance among quinolone-resistant *P. aeruginosa,* quinolone-resistant *E. coli* and MRSA among U.S. hospitals on the Mexican border (Benoit, Ellingson, Waterman, & Pearson, 2014). Other differences in antibiotic resistance trends may also exist, however, without increased knowledge on this subject matter, these findings may remain hidden.

Chapter 3: Goals and Objectives

The main goal of this study is to increase knowledge of antibiotic resistance and antibiotic consumption trends in the U.S.-Mexico border region. The three major objectives of this study are; 1.) To examine the trends in antibiotic resistance among *E. coli*, ESBL producing *E. coli*, *P. aeruginosa*, *S. aureus*, and MRSA over a 3-year period (2013, 2014, 2015) in a U.S.-Mexico border area hospital; 2.) To examine the trends in antibiotic consumption among aztreonam, cefazolin, cefepime, ceftriaxone, ciprofloxacin, gentamicin, and levofloxacin over a 3-year period (2013, 2014, 2015) in a U.S.-Mexico border area hospital; 3.) To determine if a correlation exists between the consumption of these antibiotics and antibiotic resistance trends seen in a U.S.-Mexico border area hospital.

Chapter 4: Hypotheses

The working hypotheses for this study are that there will be decreasing trends in susceptibility over time among all antibiotic-microorganism combinations analyzed and that there will be a positive correlation between antibiotic consumption and time among all antibiotics analyzed. Additionally, it was hypothesized that there will be a negative correlation between the consumption of antibiotics and the susceptibility of the microorganisms analyzed.

Chapter 5: Methods and Materials

This study employed a retrospective analysis of antibiotic resistance and antibiotic consumption secondary data in a small border area hospital in El Paso, Texas to determine if a correlation existed between the two variables for the time-period of 2013-2015. An Institutional Review Board (IRB) exemption application was submitted for this study in January of 2016 since the study involved no human subjects and only de-identified secondary data would be utilized. The University of Texas at El Paso (UTEP) IRB approved this study in February of 2016 and the hospital research committee approved this study in December of 2016.

Antibiotic resistance data

Antibiotic resistance data was obtained through the hospital antibiograms, which are compiled every six months utilizing the Clinical and Laboratory Standards Institute Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data; Approved Guideline (Clinical and Laboratory Standards Institute, 2014). These antibiograms contain the aggregate percent susceptibility (%S) for select species of bacteria for a given time-period. The antibiograms are compiled every six months to encompass the susceptibility profiles from bacteria identified for the period of January through June and July through December for the years 2013-2015. Only susceptibility profiles from the first isolate of a species of bacteria per patient per reporting period is included in the antibiograms to avoid duplicate analysis. Susceptibility profiles from bacteria identified from diagnostic samples are included in these antibiograms only. Susceptibility profiles from bacteria identified from samples collected for surveillance purposes are not included in the antibiograms. Aztreonam and the cephalosporins were excluded from analysis for ESBL producing *E. coli* because these antibiotics were automatically reported as resistant if an *E. coli* isolate was positive for the ESBL enzyme.

Antibiotic consumption data

Antibiotic consumption data was obtained from hospital pharmacy billing data. Billing data was used as a proxy for antibiotic consumption. The total amount of charges for select antibiotics was tabulated for the period of January through June and July through December for the years 2013-2015. The amount of charges for select antibiotics was then converted to grams (g) or million units (MU), where applicable, based on the strength and dosage form of the antibiotic charged. The defined daily dose (DDD) per 1000 patient days was then calculated using the World Health Organization ATC/DDD index that can be found at https://www.whocc.no/atc_ddd_index/ and hospital census data.

Study Design

A retrospective analysis of hospital antibiotic resistance data and antibiotic consumption data was performed by compiling the data into six month periods beginning in January of 2013 and ending in December of 2015. Analysis was performed to determine trends in antibiotic resistance and antibiotic consumption and to determine if a correlation existed between antibiotic consumption and antibiotic resistance trends. Five species of bacteria were chosen for this analysis based on clinical significance and emerging resistance concerns. Only species of bacteria with susceptibility data for $\geq$ 30 isolates were chosen for statistical validity. These bacterial species included *E. coli*, ESBL producing *E. coli*, *P. aeruginosa*, *S. aureus*, and MRSA. The susceptibility profile for these bacteria were analyzed based on the antibiotic formulary for the hospital. Only antibiotics used to treat infections from all body sites were included in the analysis. Antibiotics used to, primarily, treat urinary tract infections were excluded from the analysis. The fourteen antibiotics included in the analysis were Aztreonam, Cefazolin, Cefepime, Ceftriaxone,

Ciprofloxacin, Gentamicin, Imipenem, Piperacillin-tazobactam, Trimethoprim-sulfamethoxazole, Levofloxacin, Oxacillin, Penicillin, Tetracycline, and Vancomycin.

Statistical Analysis

Antibiotic resistance data was compiled into six month periods beginning in January of 2013 and ending in December of 2015. Each species of bacteria was analyzed for trends in resistance against each of the antibiotics included in the study according to the hospital's antibiotic formulary. The Cochran–Armitage test for trends was used to assess trends in resistance using Microsoft Excel and XLSTAT software. Increases in resistance was documented by identifying a decrease in susceptibility among each specific bacterial species and antibiotic combination over time (2013-2015). Decreases in resistance was documented by identifying an increase in susceptibility among each specific bacterial species and antibiotic combination over time (2013-2015). A p-value of <0.05 was used to indicate statistical significance. Antibiotic resistance data for *S. aureus* could not be assessed for the periods January-June of 2013 and July-December of 2013 since the antibiograms only included data for Methicillin Susceptible *S. aureus* (MSSA) and MRSA and did not include data for all *S. aureus* isolates as a separate category.

Antibiotic consumption data was compiled into six month periods beginning in January of 2013 and ending in December of 2015. The quantity of antibiotics charged was converted to grams or million units, where applicable, and then the DDD/1000 patient days was derived. Antibiotics were assessed for trends in consumption if a trend in resistance was found when evaluating antibiotic resistance trends among the select species of bacteria using the Cochran–Armitage test for trends. The DDD for penicillin and trimethoprim-sulfamethoxazole could not be calculated as the billing data did not contain the exact dosage and strength for these particular antibiotics. Additionally, some antibiotics (Tetracycline, Oxacillin, Imipenem) were not billed for during the

study period or for a particular period and the DDD could not be calculated. Spearman correlation test was used to assess for trends in antibiotic consumption over time (2013-2015) due one of the variables (time) being ordinal using Microsoft Excel and XLSTAT software. A correlation coefficient value of $0.6 \leq R \leq 1$ indicated a positive correlation, a correlation coefficient value of $-1 \leq R \leq -0.6$ indicated a negative correlation, and a correlation coefficient value of $R=0$ or $-0.6 < R < 0.6$ indicated no correlation if the p-value was statistically significant (p-value <0.05).

The correlation of antibiotic resistance and antibiotic consumption was assessed for bacteria exhibiting a trend in resistance regardless if a trend in antibiotic consumption, for the particular antibiotic, was identified. Spearman or Pearson correlation test was used to assess for correlations of antibiotic resistance and antibiotic consumption over time (2013-2015) depending on the normality of the distribution of antibiotic resistance and antibiotic consumption data using Microsoft Excel and XLSTAT software. Normality of the data was indicated if the value for skewness (Fisher) was between -1 and 1. A correlation coefficient value of $0.6 \leq R \leq 1$ indicated a positive correlation, a correlation coefficient value of $-1 \leq R \leq -0.6$ indicated a negative correlation, and a correlation coefficient value of $R=0$ or $-0.6 < R < 0.6$ indicated no correlation if the p-value was statistically significant (p-value <0.05).

Chapter 6: Results

Descriptive statistics

Descriptive statistics analysis for antibiotic resistance data included the number of isolates for the various bacterial species analyzed, the percent susceptibility (Table 1), and assessment of normality for the susceptibility of the various bacterial species to the antibiotics of analysis. Assessment of normality of the susceptibility data was determined after analysis of trends in antibiotic resistance for only the bacteria-antibiotic combinations that demonstrated trends in resistance and are referenced later in the results section.

Descriptive statistics analysis for antibiotic consumption data included the DDD/1000 patient days (Table 2) and assessment of normality for the of the various antibiotics of analysis. Assessment of normality of the antibiotic consumption data was determined after analysis of trends in antibiotic resistance for only the bacteria-antibiotic combinations that demonstrated trends in resistance and are referenced later in the results section.

Table 1: Percent Susceptibilities for the Bacterial Species Analyzed, 2013-2015

Organism/Antibiotic	% Susceptibility					
	Jan-Jun 2013	Jul-Dec 2013	Jan-Jun 2014	Jul-Dec 2014	Jan-Jun 2015	Jul-Dec 2015
E. coli	n=448	n=472	n=452	n=580	n=534	n=608
Aztreonam	99	100	93	93	93	90
Cefazolin	94	95	89	88	88	86
Cefepime	99	100	93	93	93	90
Ceftriaxone	99	99	93	92	93	90
Ciprofloxacin	80	81	75	74	74	74
Gentamicin	90	90	88	88	91	91
Imipenem	100	100	100	99	100	100
Piperacillin-Tazobactam	95	96	96	96	95	95
Trimethoprim-sulfamethoxazole	66	67	66	67	67	65
ESBL *E.coli*	n=30	n=43	n=32	n=42	n=41	n=59
Ciprofloxacin	0	12	3	5	2	5
Gentamicin	33	47	53	41	78	58
Imipenem	100	100	100	98	100	100
Piperacillin-Tazobactam	77	91	91	86	88	81
Trimethoprim-sulfamethoxazole	33	37	29	41	29	34
P. aeruginosa	n=66	n=105	n=107	n=95	n=89	n=131
Aztreonam	62	65	60	72	62	65
Cefepime	88	90	86	90	94	84
Ciprofloxacin	80	73	68	78	75	75
Gentamicin	77	84	77	86	89	85
Imipenem	91	90	87	86	92	87
Piperacillin-Tazobactam	89	87	78	92	91	82
S. aureus	NA	NA	n=306	n=254	n=320	n=260
Ciprofloxacin	NA	NA	73	78	83	78
Gentamicin	NA	NA	99	97	98	98
Levofloxacin	NA	NA	74	78	84	79
Oxacillin	NA	NA	76	73	80	74
Penicillin	NA	NA	10	15	15	16
Tetracycline	NA	NA	95	94	96	97
Vancomycin	NA	NA	100	100	100	100
MRSA	n=89	n=68	n=74	n=66	n=64	n=69
Ciprofloxacin	33	32	19	30	34	38
Gentamicin	98	99	97	91	97	94
Levofloxacin	33	32	22	30	34	28
Tretracycline	96	97	95	94	95	97
Trimethoprim-sulfamethoxazole	100	100	96	97	97	99
Vancomycin	100	100	100	100	100	100

NA= Data unavailable

Table 2: Defined Daily Dose per 1000 Patient Days, 2013-2015

Antibiotic	DDD/1000 patient days					
	Jan-Jun 2013	Jul-Dec 2013	Jan-Jun 2014	Jul-Dec 2014	Jan-Jun 2015	Jul-Dec 2015
Aztreonam	1.9	5.1	1.4	2.4	1.5	1.2
Cefazolin	38.1	40.8	44.6	37.1	36.1	48.6
Cefepime	21.0	27.6	24.6	33.6	39.4	25.7
Ceftriaxone	80.6	85.7	82.5	81.7	88.9	96.3
Ciprofloxacin	27.7	17.3	19.0	21.2	14.7	14.2
Gentamicin	17.2	22.8	9.6	7.7	9.1	13.4
Imipenem	0.7	0.05	0.1	0.3	–	–
Piperacillin-Tazobactam	186	179.3	188.5	223.2	244.1	227.7
Trimethoprim-sulfamethoxazole	NA	NA	NA	NA	NA	NA
Levofloxacin	177.3	160.2	172.6	137.8	140.6	128.7
Oxacillin	–	–	–	–	–	–
Penicillin	NA	NA	NA	NA	NA	NA
Tetracycline	–	–	–	–	–	–
Vancomycin	48	96.6	79.5	58.2	71.1	61.2

No charges existed for tetracycline, oxacillin, and imipenem for the periods indicated by a dash

NA= Data unavailable. Unable to calculate due to the lack of dosage information contained in the billing data

Inferential statistics

Antibiotic resistance data was analyzed for trends in resistance over time using the Cochran-armitage test for trends (Table 3 and Table 4). Statistically significant increases in resistance were identified for *E. coli* against the following antibiotics: aztreonam (p-value <0.0001), cefazolin (p-value <0.0001), cefepime (p-value <0.0001), ceftriaxone (p-value <0.0001), and ciprofloxacin (p-value 0.001). A statistically significant increase in resistance for MRSA against gentamicin was also identified (p-value 0.044). Statistically significant decreases in resistance were identified for ESBL producing *E. coli* against gentamicin (p-value 0.002) and for *S. aureus* against the following antibiotics: ciprofloxacin (p-value 0.023), levofloxacin (p-value 0.018), and penicillin (p-value 0.021).

Antibiotic consumption data was converted into the DDD/1000 patient days and analyzed by the Spearman correlation test (Table 5). Antibiotics were only analyzed for trends in consumption if a trend in resistance was identified for a bacterial species to that particular

antibiotic. The only trend identified was a negative correlation between time and levofloxacin consumption for the study period (Spearman correlation R= -0.886, p-value 0.033).

The correlation of antibiotic resistance (%S) and antibiotic consumption (DDD/1000 patient days) was assessed for bacteria exhibiting a trend in resistance regardless if a trend in antibiotic consumption, for the particular antibiotic, was identified (Table 6). Spearman or Pearson correlation test was used to assess for correlations of antibiotic resistance and antibiotic consumption depending on the normality of the distribution of antibiotic resistance and antibiotic consumption data. The normality of antibiotic resistance data (%S) for *E. coli* to aztreonam (skewness value 0.580), cefazolin (skewness value 0.676), cefepime (skewness value 0.580), ceftriaxone (skewness value 0.581), ciprofloxacin (skewness value 0.951), and gentamicin (skewness value -0.523) was normal. The normality of antibiotic resistance data (%S) for *S. aureus* to ciprofloxacin (skewness value 0.00) and levofloxacin (skewness value 0.356) was also normal. The normality of antibiotic resistance data (%S) for MRSA to gentamicin (skewness value -1.103) was abnormal. The normality of antibiotic consumption data (DDD/1000 patient days) for cefazolin (skewness value 0.849), cefepime (skewness value 0.819), gentamicin (skewness value 0.948) and levofloxacin (skewness value 0.123) was normal and abnormal for aztreonam (skewness value 2.017), ceftriaxone (skewness value 1.257), and ciprofloxacin (skewness value 1.124). Spearman correlation was used to assess for correlations if one of the variables (%S or DDD/1000 patient days) exhibited an abnormal distribution. Pearson correlation was used to assess for correlations if both variables (%S and DDD/1000 patient days) exhibited a normal distribution. No correlations were identified between any of the %S of the bacterial species and the antibiotic consumption data (DDD/1000 patient days) analyzed.

Table 3: Bacterial Species Exhibiting a Decrease in Susceptibility (Increase in Resistance), 2013-2015

Organism/Antibiotic	% Susceptibility (n)						p-value (lower-tailed)
	Jan-Jun 2013	Jul-Dec 2013	Jan-Jun 2014	Jul-Dec 2014	Jan-Jun 2015	Jul-Dec 2015	
E. coli	n=448	n=472	n=452	n=580	n=534	n=608	
Aztreonam	99	100	93	93	93	90	<0.0001
Cefazolin	94	95	89	88	88	86	<0.0001
Cefepime	99	100	93	93	93	90	<0.0001
Ceftriaxone	99	99	93	92	93	90	<0.0001
Ciprofloxacin	80	81	75	74	74	74	0.001
MRSA	n=89	n=68	n=74	n=66	n=64	n=69	
Gentamicin	98	99	97	91	97	94	0.044

Table 4: Bacterial Species Exhibiting an Increase in Susceptibility (Decrease in Resistance), 2013-2015

Organism/Antibiotic	% Susceptibility (n)						p-value (upper-tailed)
	Jan-Jun 2013	Jul-Dec 2013	Jan-Jun 2014	Jul-Dec 2014	Jan-Jun 2015	Jul-Dec 2015	
ESBL *E. coli*	n=30	n=43	n=32	n=42	n=41	n=59	
Gentamicin	33	47	53	41	78	58	0.002
S. aureus			n=306	n=254	n=320	n=260	
Ciprofloxacin	NA	NA	73	78	83	78	0.023
Levofloxacin	NA	NA	74	78	84	79	0.018
Penicillin	NA	NA	10	15	15	16	0.021

NA= Data unavailable

Table 5: Correlation Between Time and Antibiotic Consumption for Antibiotics where Bacterial Trends in Susceptability was Identified, 2013-2015

Antibiotic	DDD/1000 patient days						R	p-value
	Jan-Jun 2013	Jul-Dec 2013	Jan-Jun 2014	Jul-Dec 2014	Jan-Jun 2015	Jul-Dec 2015		
Aztreonam	1.9	5.1	1.4	2.4	1.5	1.2	-0.600	0.242
Cefazolin	38.1	40.8	44.6	37.1	36.1	48.6	0.086	0.919
Cefepime	21.0	27.6	24.6	33.6	39.4	25.7	0.543	0.297
Ceftriaxone	80.6	85.7	82.5	81.7	88.9	96.3	0.771	0.103
Ciprofloxacin	27.7	17.3	19.0	21.2	14.7	14.2	-0.771	0.103
Gentamicin	17.2	22.8	9.6	7.7	9.1	13.4	-0.543	0.297
Levofloxacin	177.3	160.2	172.6	137.8	140.6	128.7	-0.886	0.033

Table 6: Correlation of Antibiotic Consumption and Antibiotic Resistance for Bacterial Species Exhibiting a Trend in Susceptibility, 2013-2015

Antibiotic	*E.coli*		MRSA		*S. aureus*	
	R	p-value	R	p-value	R	p-value
Aztreonam	0.820	0.058	–	–	–	–
Cefazolin	-0.328	0.525	–	–	–	–
Cefepime	-0.337	0.514	–	–	–	–
Ceftriaxone	-0.471	0.356	–	–	–	–
Ciprofloxacin	0.395	0.497	–	–	-0.316	0.750
Gentamicin	0.366	0.476	0.812	0.058	–	–
Levofloxacin	–	–	–	–	-0.647	0.353

No trends in resistance were identified for the bacterial species-antibiotic combination indicated by a dash

Chapter 7: Discussion

Antibiotic resistance due to the excessive use of antibiotics is a growing public health threat. Geographical, cultural and other unique differences in the U.S.-Mexico border region can contribute to antibiotic resistance trends not seen in other parts of the U.S. Antibiotic resistance and antibiotic consumption studies in the U.S.-Mexico border region are rare, however. Without increased antibiotic resistance and consumption surveillance data, important findings can be missed in this unique region. The goal of this study was to increase knowledge of antibiotic resistance and antibiotic consumption trends in the U.S.-Mexico border region. This study identified statistically significant increases in resistance among *E. coli* to aztreonam, cefazolin, cefepime, ceftriaxone, and ciprofloxacin. Additionally, a statistically significant increase in resistance among MRSA to gentamicin was also identified for the study period. Statistically significant decreases in resistance were identified for ESBL producing *E. coli* to gentamicin and for *S. aureus* to ciprofloxacin, levofloxacin, and penicillin. The only trend in antibiotic consumption identified was a negative correlation between time and levofloxacin consumption for the study period. No correlations between any of the %S of the bacterial species and the antibiotic consumption data (DDD/1000 patient days) analyzed were identified.

This study's finding of increasing resistance among *E.coli* to ceftriaxone and ciprofloxacin compares similar to the U.S. as a whole. Rates of resistance among *E.coli* to the third-generation generation cephalosporins and fluoroquinolones have been increasing well over the last decade. The % susceptibility of *E.coli* to third-generation generation cephalosporins and fluoroquinolones has decreased from 98% in 1999 to 84% in 2014 and from 95% in 1999 to 65% in 2014, respectively (p-value <0.0001, p-value <0.0001) (Center for Disease Dynamics Economics & Policy, 2017). Antibiotic resistance studies on the U.S.-Mexico border are rare,

however, one study did identify a statistically significant increase in resistance among *E.coli* to third-generation cephalosporins and fluoroquinolones in the U.S.-Mexico border (Benoit et al., 2014). A recent study of U.S. Department of Defense hospitals identified a positive correlation among *E.coli* ciprofloxacin resistance and ciprofloxacin prescription rates (Spearman correlation R= 0.53, p-value 0.01) (Spencer, Milburn, & Chukwuma, 2016). Although this thesis study did not find any correlation between antibiotic consumption and resistance rates for any of the bacterial species analyzed, increases in resistance could be due to the presence of resistant genes already circulating in the study hospital or community. Interesting findings with this thesis study were the identification of increases in susceptibility among *S.aureus* to ciprofloxacin, levofloxacillin, and penicillin. The increase in susceptibility of *S.aureus* to penicillin has been found in other studies in the U.S. (Chabot, Stefan, Friderici, Schimmel, & Larioza, 2015; Kanjilal et al., 2017). Although the correlation between penicillin consumption and penicillin resistance in *S.aureus* could not be determined in this thesis study, a decrease in penicillin usage could be related to this trend. *S.aureus* is highly resistant to penicillin and physicians at the study hospital may avoid prescribing this antibiotic for this bacterial species due to this fact. Penicillin should be considered for penicillin susceptible *S.aureus* as this antibiotic has several advantages due to its narrow spectrum of activity and lack of association with CDI (Chabot et al., 2015). Although no correlation between the %S of *S.aureus* to levofloxacin consumption was identified, levofloxacin consumption did decrease at this hospital and may have contributed to the increase in susceptibility of *S.aureus* to levofloxacin.

This study is subject to a few limitations. First, billing data was used as a proxy for antibiotic consumption and may not accurately reflect actual antibiotic consumption by individuals at this hospital. Medication administration records are preferable to pharmacy billing

data; however, these are more difficult to access. Second, the metric chosen for antibiotic consumption (DDD) is limited in that this metric is not appropriate for children and it can underestimate antibiotic consumption if the actual administered dose differs from the WHO DDD (Schechner, Temkin, Harbarth, Carmeli, & Schwaber, 2013). Third, the study period of three years may be too small a window to identify significant trends in emerging antibiotic resistance patterns. Resistance to antibiotics may arise shortly after the introduction of an antibiotic or may take decades as in the case of vancomycin-resistant *S.aureus* (Zaman et al., 2017). This fact highlights the importance of continuous antibiotic resistance surveillance efforts in order to identify new antibiotic resistance patterns. There are several strengths associated with this study. First, this study is the only study that assessed both trends in antibiotic resistance and antibiotic consumption on the U.S.-Mexico border to determine correlations between the two variables. Other studies lacked the antibiotic consumption component. Second, this thesis study examined subpopulations of *E.coli* and *S.aureus* (MRSA, ESBL *E.coli*) to a variety of antibiotics and not just one. This thesis study also has several implications for public and border health. The increase in resistance of *E.coli* to the cephalosporins and fluoroquiolones analyzed is a serious concern corroborated by other U.S. and U.S.-Mexico border studies. Although this study may not be generalizable to other hospitals in the U.S.-Mexico border region, it provides pre-intervention data for comparison against future ASP implementation at the study hospital. Tracking trends in resistance is an important aspect of managing antibiotic resistance at any hospital. Local public health departments may also be interested in this data as it provides a snapshot of antibiotic resistance patterns in this region. City-wide antibiotic resistance surveillance could be achievable as most, if not all, hospitals produce antibiograms annually or semi-annually.

The Master of Public Health program at UTEP integrates five core Hispanic and border health competencies into the coursework for this degree. These include: biostatistics, environmental health, epidemiology, health policy and management, and social and behavioral sciences. The integration of four of these competencies was included in this thesis study. Biostatistics was utilized to analyze data related to antibiotic resistance and consumption in the U.S.-Mexico border and then to make meaningful conclusions based on this analysis. The data used for this study was epidemiological in nature and when combined with biostatistics, important epidemiological trends in antibiotic resistance were identified in the U.S.-Mexico border. This study also acknowledged the behavioral and cultural practices that could possibly contribute to unique antibiotic resistance and consumption trends in the U.S.-Mexico border region. Lastly, this study provides data that can be used in the development of health policy such as with the implementation of ASPs at the study hospital or with the implementation of city-wide antibiotic resistance monitoring.

References

Baggs, J., Fridkin, S. K., Pollack, L. A., Srinivasan, A., & Jernigan, J. A. (2016). EStimating national trends in inpatient antibiotic use among us hospitals from 2006 to 2012. *JAMA Internal Medicine*. doi:10.1001/jamainternmed.2016.5651

Barnett, J., & Berchick, E. (2017). *Health Insurance Coverage in the United States: 2016*. Retrieved from https://www.census.gov/library/publications/2017/demo/p60-260.html

Benoit, S. R., Ellingson, K. D., Waterman, S. H., & Pearson, M. L. (2014). Antimicrobial resistance in eight US hospitals along the US-Mexico border, 2000-2006. *Epidemiol Infect, 142*(11), 2378-2387. doi:10.1017/s095026881300318x

Bureau of Transportation Statistics. (2017). Border Crossing Entry Data. Retrieved from https://www.bts.gov/content/border-crossingentry-data

Canton, R., Horcajada, J. P., Oliver, A., Garbajosa, P. R., & Vila, J. (2013). Inappropriate use of antibiotics in hospitals: the complex relationship between antibiotic use and antimicrobial resistance. *Enferm Infecc Microbiol Clin, 31 Suppl 4*, 3-11. doi:10.1016/s0213-005x(13)70126-5

Center for Disease Dynamics Economics & Policy. (2017). ResistanceMap- Antibiotic resistance. Retrieved from https://resistancemap.cddep.org/AntibioticResistance.php

Centers for Disease Control and Prevention. (2013). *Antibiotic Resistance Threats in the United States, 2013*. Retrieved from Atlanta, Georgia:

Centers for Disease Control and Prevention. (2014). *Core Elements of Hospital Antibiotic Stewardship Programs*. Retrieved from Atlanta, Georgia:

Chabot, M. R., Stefan, M. S., Friderici, J., Schimmel, J., & Larioza, J. (2015). Reappearance and treatment of penicillin-susceptible Staphylococcus aureus in a tertiary medical centre. *Journal of Antimicrobial Chemotherapy, 70*(12), 3353-3356. doi:10.1093/jac/dkv270

Clinical and Laboratory Standards Institute. (2014). M39-A4 Analysis and Presentation of Cumulative Antimicrobial Susceptability Test Data; Approved Guideline (4th ed.). Wayne, PA: Clinical and Laboratory Standards Institute,.

Cloete, T. E. (2003). Resistance mechanisms of bacteria to antimicrobial compounds. *International Biodeterioration & Biodegradation, 51*(4), 277-282. doi:http://dx.doi.org/10.1016/S0964-8305(03)00042-8

Dantes, R., Mu, Y., Hicks, L. A., Cohen, J., Bamberg, W., Beldavs, Z. G., . . . Lessa, F. C. (2015). Association Between Outpatient Antibiotic Prescribing Practices and Community-Associated Clostridium difficile Infection. *Open Forum Infectious Diseases, 2*(3), ofv113. doi:10.1093/ofid/ofv113

Dellit, T. H., Owens, R. C., McGowan, J. E., Gerding, D. N., Weinstein, R. A., Burke, J. P., . . . Hooton, T. M. (2007). Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. *Clinical Infectious Diseases, 44*(2), 159-177. doi:10.1086/510393

Dempsey, P. P., Businger, A. C., Whaley, L. E., Gagne, J. J., & Linder, J. A. (2014). Primary care clinicians' perceptions about antibiotic prescribing for acute bronchitis: a qualitative study. *BMC Family Practice, 15*(1), 194. doi:10.1186/s12875-014-0194-5

Fleming-Dutra, K. E., Hersh, A. L., Shapiro, D. J., Bartoces, M., Enns, E. A., File, T. M., Jr., . . . Hicks, L. A. (2016). Prevalence of Inappropriate Antibiotic Prescriptions Among US

Ambulatory Care Visits, 2010-2011. *JAMA, 315*(17), 1864-1873. doi:10.1001/jama.2016.4151

Giedraitiene, A., Vitkauskiene, A., Naginiene, R., & Pavilonis, A. (2011). Antibiotic resistance mechanisms of clinically important bacteria. *Medicina (Kaunas), 47*(3), 137-146.

Hatam, N., Askarian, M., Moravveji, A. R., & Assadian, O. (2011). Economic burden of inappropriate antibiotic use for prophylactic purpose in shiraz, iran. *Iranian Red Crescent medical journal, 13*(4), 234-238.

Hecker, M. T., Aron, D. C., Patel, N. P., Lehmann, M. K., & Donskey, C. J. (2003). Unnecessary use of antimicrobials in hospitalized patients: Current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. *Archives of Internal Medicine, 163*(8), 972-978. doi:10.1001/archinte.163.8.972

Homedes, N., & Ugalde, A. (2012). Mexican Pharmacies and Antibiotic Consumption at the US-Mexico Border. *Southern med review, 5*(2), 9-19.

Ingram, P. R., Seet, J. M., Budgeon, C. A., & Murray, R. (2012). Point-prevalence study of inappropriate antibiotic use at a tertiary Australian hospital. *Intern Med J, 42*(6), 719-721. doi:10.1111/j.1445-5994.2012.02809.x

Kaki, R., Elligsen, M., Walker, S., Simor, A., Palmay, L., & Daneman, N. (2011). Impact of antimicrobial stewardship in critical care: a systematic review. *Journal of Antimicrobial Chemotherapy, 66*(6), 1223-1230. doi:10.1093/jac/dkr137

Kanjilal, S., Sater, M. R. A., Thayer, M., Lagoudas, G. K., Kim, S., Blainey, P. C., & Grad, Y. H. (2017). Trends in antibiotic susceptibility in Staphylococcus aureus in Boston, Massachusetts, 2000-2014. *Journal of Clinical Microbiology*. doi:10.1128/jcm.01160-17

Landers, T. F., Cohen, B., Wittum, T. E., & Larson, E. L. (2012). A Review of Antibiotic Use in Food Animals: Perspective, Policy, and Potential. *Public Health Reports, 127*(1), 4-22.

Lee, G. C., Reveles, K. R., Attridge, R. T., Lawson, K. A., Mansi, I. A., Lewis, J. S., 2nd, & Frei, C. R. (2014). Outpatient antibiotic prescribing in the United States: 2000 to 2010. *BMC Med, 12*, 96. doi:10.1186/1741-7015-12-96

Lim, D., & Strynadka, N. C. J. (2002). Structural basis for the β lactam resistance of PBP2a from methicillin-resistant Staphylococcus aureus. *Nature Structural Biology, 9*(11), 870.

May, L., Gudger, G., Armstrong, P., Brooks, G., Hinds, P., Bhat, R., . . . Rand, C. (2014). Multisite Exploration of Clinical Decision-Making for Antibiotic Use by Emergency Medicine Providers Using Quantitative and Qualitative Methods. *Infection Control and Hospital Epidemiology, 35*(9), 1114-1125. doi:10.1086/677637

McHugh, S. M., Collins, C. J., Corrigan, M. A., Hill, A. D. K., & Humphreys, H. (2011). The role of topical antibiotics used as prophylaxis in surgical site infection prevention. *Journal of Antimicrobial Chemotherapy, 66*(4), 693-701. doi:10.1093/jac/dkr009

Michigan State University. (2011). Antimicrobial Resistance Learning Site. Retrieved from http://amrls.cvm.msu.edu/microbiology

Mier, N., Ory, M. G., Zhan, D., Conkling, M., Sharkey, J. R., & Burdine, J. N. (2008). Health-related quality of life among Mexican Americans living in colonias at the Texas-Mexico border. *Soc Sci Med, 66*(8), 1760-1771. doi:10.1016/j.socscimed.2007.12.017

Nowak, M. A., Nelson, R. E., Breidenbach, J. L., Thompson, P. A., & Carson, P. J. (2012). Clinical and economic outcomes of a prospective antimicrobial stewardship program. *Am J Health Syst Pharm, 69*(17), 1500-1508. doi:10.2146/ajhp110603

Rawat, D., & Nair, D. (2010). Extended-spectrum β-lactamases in Gram Negative Bacteria. *Journal of Global Infectious Diseases, 2*(3), 263-274. doi:10.4103/0974-777X.68531

Rivera, J. O., Ho, H., Dominguez, D. C., Tyroch, A. H., Antony, S., Norte, A., & Perez-Ruvalcaba, J. A. (2009). Study of methicillin-resistant Staphylococcus aureus on the U.S./Mexico border. *Travel Med Infect Dis, 7*(1), 30-34. doi:10.1016/j.tmaid.2008.12.005

Schechner, V., Temkin, E., Harbarth, S., Carmeli, Y., & Schwaber, M. J. (2013). Epidemiological Interpretation of Studies Examining the Effect of Antibiotic Usage on Resistance. *Clinical Microbiology Reviews, 26*(2), 289-307. doi:10.1128/cmr.00001-13

Spencer, J. R., Milburn, E. K., & Chukwuma, U. (2016). Correlation between antimicrobial resistance in Escherichia coli infections in hospitalized patients and rates of inpatient prescriptions for selected antimicrobial agents, Department of Defense hospitals, 2010-2014. *Msmr, 23*(3), 6-10.

Su, D., Pratt, W., Stimpson, J. P., Wong, R., & Pagán, J. A. (2014). Uninsurance, Underinsurance, and Health Care Utilization in Mexico by US Border Residents. *Journal of immigrant and minority health / Center for Minority Public Health, 16*(4), 607-612. doi:10.1007/s10903-013-9828-2

Szymczak, J. E., Feemster, K. A., Zaoutis, T. E., & Gerber, J. S. (2014). Pediatrician Perceptions of an Outpatient Antimicrobial Stewardship Intervention. *Infection Control and Hospital Epidemiology, 35*(S3), S69-S78. doi:10.1086/677826

Tamma, P. D., Cosgrove, S. E., & Maragakis, L. L. (2012). Combination therapy for treatment of infections with gram-negative bacteria. *Clin Microbiol Rev, 25*(3), 450-470. doi:10.1128/cmr.05041-11

Tenover, F. C. (2006). Mechanisms of antimicrobial resistance in bacteria. *Am J Infect Control, 34*(5, Supplement), S3-S10. doi:http://dx.doi.org/10.1016/j.ajic.2006.05.219

Texas Department of State Health Services. (2013). Texas Health Data Center for Health Statistics. http://healthdata.dshs.texas.gov/HealthFactsProfiles

Texas Medical Association. (2017). The Uninsured in Texas. Retrieved from https://www.texmed.org/Uninsured_in_Texas/

The AIDS Education and Training Center. (2014). Overview of HIV/AIDS in the Texas-Mexico Border Region 2014. Retrieved from https://www.aidsetc.org/border/profile-texas

Van Boeckel, T. P., Brower, C., Gilbert, M., Grenfell, B. T., Levin, S. A., Robinson, T. P., . . . Laxminarayan, R. (2015). Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences, 112*(18), 5649-5654. doi:10.1073/pnas.1503141112

Wenisch, J. M., Equiluz-Bruck, S., Fudel, M., Reiter, I., Schmid, A., Singer, E., & Chott, A. (2014). Decreasing Clostridium difficile Infections by an Antimicrobial Stewardship Program That Reduces Moxifloxacin Use. *Antimicrob Agents Chemother, 58*(9), 5079-5083. doi:10.1128/aac.03006-14

Zaman, S. B., Hussain, M. A., Nye, R., Mehta, V., Mamun, K. T., & Hossain, N. (2017). A Review on Antibiotic Resistance: Alarm Bells are Ringing. *Cureus, 9*(6), e1403. doi:10.7759/cureus.1403

Zoorob, R., Grigoryan, L., Nash, S., & Trautner, B. W. (2016). Non-prescription antimicrobial use in a primary care population in the United States: evidence for action. *Antimicrob Agents Chemother*. doi:10.1128/aac.00528-16

Vita

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He began his career as a Medical Technologist generalist at The Hospitals of Providence (THOP) East Campus in April of 2008 where he worked in all areas of the laboratory including the chemistry, hematology, blood bank, and microbiology section. After four years in this position, he was promoted to the Lead Medical Technologist in charge of the microbiology section of the laboratory at this facility. In February of 2015 Christopher began working with the Infection Prevention department at THOP East Campus concurrent with his position as Lead Medical Technologist.

In February of 2016, Christopher accepted the Public Health Laboratory Manager position with the El Paso Department of Public Health (EPDPH) where he opened a STAT laboratory, implemented Zika, chikungunya, and dengue PCR testing, and consolidated two EPDPH laboratory locations for improved efficiency.

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